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PHARMACEUTICAL COMPOSITION OF HIV-PROTEASE INHIBITORS

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(57) In accordance with the present invention, there is a pharmaceutical composition comprising a solution of an HIV protease inhibiting compound (preferably, a compound of the formula II) in a pharmaceutically acceptable organic solvent or a mixture of pharmaceutically acceptable organic solvents, the solvent comprising a pharmaceutically acceptable alcohol.

Also in accordance with the present invention, there is a pharmaceutical composition comprising a solution of an HIV protease inhibiting compound (preferably, a compound of the formula II) in a pharmaceutically acceptable organic solvent or a mixture of pharmaceutically acceptable organic solvents, the solvent comprising a pharmaceutically acceptable alcohol, wherein the solution is encapsulated in a soft elastic gelatin capsule (SEC) or a hard gelatin capsule.

In particular, in a first form the invention provides a pharmaceutical composition comprising a solution of (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane in a pharmaceutically acceptable organic solvent, the solvent comprising a pharmaceutically acceptable alcohol.

Claim

1. A pharmaceutical composition comprising a solution of (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)-valinyl)amino)-2-(N-((5-thiazolyl)methoxy-carbonyl)amino)-1,6-diphenyl-3-hydroxyhexane in a pharmaceutically acceptable organic solvent, the solvent comprising a pharmaceutically acceptable alcohol.

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(54) Title: PHARMACEUTICAL COMPOSITION OF HIV-PROTEASE INHIBITORS

(57) Abstract

A pharmaceutical composition is disclosed which comprises a solution of an HIV protease inhibiting compound in a pharmaceutically acceptable organic solvent comprising a pharmaceutically acceptable alcohol. The composition can optionally comprise a pharmaceutically acceptable acid or a combination of pharmaceutically acceptable acids. The solution can optionally be encapsulated in hard gelating capsule or soft elastic gelating capsules. The solution can optionally be granulated with a pharmaceutically acceptable granulating agent.

PHARMACEUTICAL COMPOSITION OF HIV-PROTEASE INHIBITORS

This is a continuation-in-part of U.S. patent application Serial No. 267,331, filed June 28, 1994, which is a continuation-in-part of U.S. patent application Serial No. 188,511, filed January 28, 1994, which is a continuation-in-part of U.S. patent application Serial No. 120,886, filed September 13, 1993.

Technical Field

A liquid, semi-solid or solid pharmaceutical composition providing improved oral bioavailability is disclosed for compounds which are inhibitors of HIV protease (in particular, HIV-1 and HIV-2 protease). In particular, the composition comprises a solution of the HIV protease inhibitor in a pharmaceutically acceptable organic solvent or a mixture of pharmaceutically acceptable organic solvents, the solvent comprising a pharmaceutically acceptable alcohol. The composition can optionally be granulated by mixing with a pharmaceutically acceptable granulating agent or mixture of granulating agents. The composition can optionally be encapsulated in either hard gelatin capsules or soft elastic capsules (SEC).

Background of the Invention

One measure of the potential usefulness of an oral dosage form of a new pharmaceutical agent is the bioavailability observed after oral administration of the dosage form. Various factors can affect the bioavailability of a drug when administered orally. These factors include aqueous solubility, drug absorption throughout the gastrointestinal tract, dosage strength and first pass effect. Aqueous solubility is one of the most important of these factors. When a drug has poor aqueous solubility, attempts are often made to identify salts or other derivatives of the drug which have improved aqueous solubility. When a salt or other derivative of the drug is identified which has good aqueous solubility, it is generally accepted that an aqueous solution formulation of this salt or derivative

will provide the optimum oral bioavailability. The bioavailability of the aqueous oral solution formulation of a drug is then generally used as the standard or ideal bioavailability against which other oral dosage forms are measured.

For a variety of reasons, such as patient compliance and taste masking, a solid dosage form, such as capsules, is usually preferred over a liquid dosage form. However, oral solid dosage forms of a drug generally provide a lower bioavailability than oral solutions of the drug. One goal of the development of a suitable capsule dosage form is to obtain a bioavailability of the drug that is as close as possible to the ideal bioavailability demonstrated by the oral aqueous solution formulation of the drug.

It has recently been determined that HIV protease inhibiting compounds are useful for inhibiting HIV protease in vitro and in vivo, are useful for inhibiting HIV (human immunodeficiency virus) infections and are useful for treating AIDS (acquired immunodeficiency syndrome). HIV protease inhibiting compounds typically are characterized by having poor oral bioavailability.

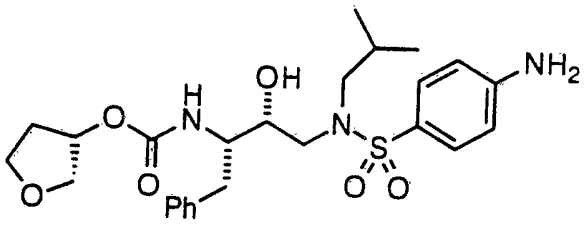
Examples of HIV protease inhibiting compounds include N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenylmethyl-4(S)-hydroxy-5-(1-(4-(3-pyridylmethyl)-2(S)-N'-(t-butylcarboxamido)-piperazinyl))-pentaneamide and related compounds, disclosed in European Patent Application No. EP541168, published May 12, 1993;

N-tert-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-[[N-(2-quinolylcarbonyl)-L-asparaginyl]amino]butyl]-(4aS,8aS)-isoquinoline-3(S)-carboxamide (i.e., saquinavir) and related compounds, disclosed in U.S. Patent No. 5,196,438, issued March 23, 1993;

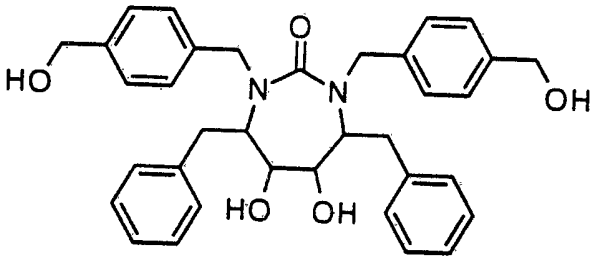
5(S)-Boc-amino-4(S)-hydroxy-6-phenyl-2(R)-phenylmethylhexanoyl-(L)-Val-(L)-Phe-morpholin-4-ylamide and related compounds, disclosed in European Patent Application No. EP532466, published March 17, 1993;

1-Naphthoxyacetyl-beta-methylthio-Ala-(2S,3S)-3-amino-2-hydroxy-4-butanoyl-1,3-thiazolidine-4-t-butylamide (i.e., 1-Naphthoxyacetyl-Mta-(2S,3S)-AHPBA-Thz-NH-tBu) and related compounds, disclosed in European Patent Application No. EP490667, published June 17, 1992;

[1S-[1R*(R*),2S*]}-N[1][3-[[[(1,1-dimethylethyl)amino]carbonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-butanediamide and related compounds, disclosed in PCT Patent Application No. WO92/08701, published May 29, 1992;

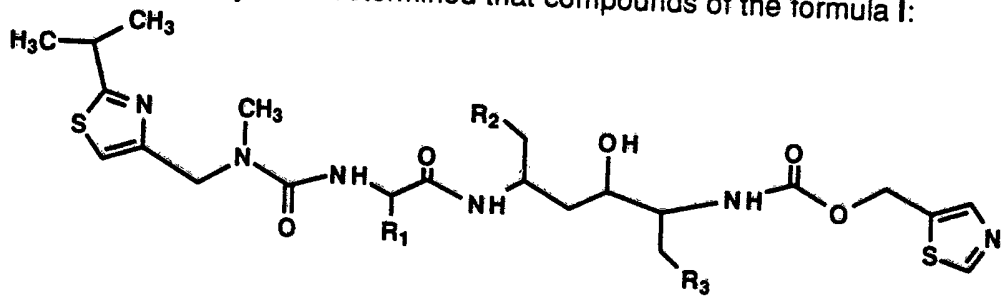


and related compounds, disclosed in PCT Patent Application No. WO94/05639, published March 17, 1994; and



and related compounds, disclosed in PCT Patent Application No. WO93/07128, published April 15, 1993.

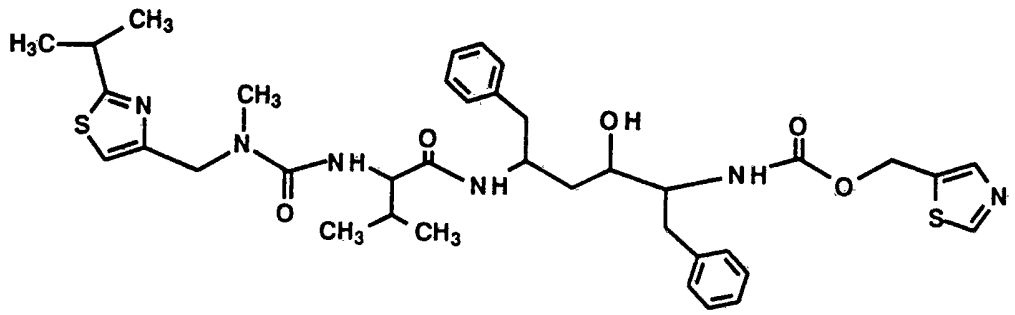
It has recently been determined that compounds of the formula I:



I

wherein R_1 is lower alkyl and R_2 and R_3 are phenyl are inhibitors of HIV-1 and HIV-2 protease and are useful to inhibit HIV infections and, thus, are useful for the treatment of AIDS.

In particular, the compound of formula **II**, has been found to be especially effective as an inhibitor of HIV-1 and HIV-2 protease.



II

The most preferred compound of formula **II** is (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane (compound **III**).

Compound **III** has an aqueous solubility of approximately 6 micrograms per milliliter at pH >2. This is considered to be extremely poor aqueous solubility and, therefore, compound **III** in the free base form would be expected to provide very low oral bioavailability. In fact, the free base form of compound **III**, administered as an unformulated solid in a capsule dosage form, is characterized by a bioavailability of less than 2% following a 5 mg/kg oral dose in dogs.

Acid addition salts of compound **III** (for example, bis-hydrochloride, bis-tosylate, bis-methane sulfonate and the like) have aqueous solubilities of <0.1 milligrams/milliliter. This is only a slight improvement over the solubility of the free base. This low aqueous solubility would not make practical the administration of therapeutic amounts of an acid addition salt of compound **III** as an aqueous solution. Furthermore, in view of this low aqueous solubility, it is not surprising that the bis-tosylate of compound **III**, administered as an unformulated

solid in a capsule dosage form, is characterized by a bioavailability of less than 2% following a 5 mg/kg oral dose in dogs.

In order to have a suitable oral dosage form of compound III, the oral bioavailability of compound III should be at least 20%. Preferably, the oral bioavailability of compound III from the dosage form should be greater than about 40% and, more preferably, greater than about 50%.

While some drugs would be expected to have good solubility in organic solvents, it would not necessarily follow that oral administration of such a solution would give good bioavailability for the drug. It has been found that compound III has good solubility in pharmaceutically acceptable organic solvents and that the solubility in such solvents is enhanced by at least four times in the presence of a pharmaceutically acceptable acid. Unexpectedly, these solutions of compound III in organic solvents provide an oral bioavailability of from about 20% to about 40% in dogs. Quite unexpectedly, administration of the solution as an encapsulated dosage form (soft elastic capsules or hard gelatin capsules) provides an oral bioavailability of as high as about 90% or more. In addition, quite unexpectedly, when certain solution compositions of compound III are granulated by mixing with a pharmaceutically acceptable granulating agent and the resulting solid composition is administered to dogs, an acceptable oral bioavailability is observed.

Disclosure of the Invention

In accordance with the present invention, there is a pharmaceutical composition comprising a solution of an HIV protease inhibiting compound (preferably, a compound of the formula II) in a pharmaceutically acceptable organic solvent or a mixture of pharmaceutically acceptable organic solvents, the solvent comprising a pharmaceutically acceptable alcohol.

Also in accordance with the present invention, there is a pharmaceutical composition comprising a solution of an HIV protease inhibiting compound (preferably, a compound of the formula II) in a pharmaceutically acceptable organic solvent or a mixture of pharmaceutically acceptable organic solvents, the solvent comprising a pharmaceutically acceptable alcohol, wherein the solution is encapsulated in a soft elastic gelatin capsule (SEC) or a hard gelatin capsule.

In particular, in a first form the invention provides a pharmaceutical composition comprising a solution of (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane in a pharmaceutically acceptable organic solvent, the solvent comprising a pharmaceutically acceptable alcohol.

In a second form, the invention provides a pharmaceutical composition comprising a solution of

(a) (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane; and

(b) a pharmaceutically acceptable acid or a combination of pharmaceutically acceptable acids in a pharmaceutically acceptable organic solvent, the solvent comprising a pharmaceutically acceptable alcohol.

AUSTRALIAN 33 PATENT OFFICE

The solution composition of the invention can also comprise from about 0 to about 3 molar equivalents (based on the amount of the HIV protease inhibiting compound in the composition) of a pharmaceutically acceptable acid or a mixture of pharmaceutically acceptable acids. Preferably, the pharmaceutically acceptable acid or mixture of pharmaceutically acceptable acids is present in a total amount of from about 0.2 to about 2.0 molar equivalents (based on the amount of the HIV protease inhibiting compound in the composition).

The solution composition of the invention can also comprise from about 0% to about 10% (by weight of the total solution) of water. In addition, the solution composition of the invention can comprise a pharmaceutically acceptable surfactant or a mixture of pharmaceutically acceptable surfactants. In addition, the solution composition of the invention can comprise an antioxidant (for example, ascorbic acid, BHA (butylated hydroxyanisole), BHT (butylated hydroxytoluene), vitamin E, vitamin E PEG 1000 succinate and the like) for chemical stability. Solutions encapsulated in a SEC may also comprise glycerin for physical stability.

The compositions of this invention (solution or encapsulated solution) provide improved oral bioavailability for compound II when compared to non-formulated compound II (base) or non-formulated compound II (acid addition salt), or even when compared to a mixed aqueous/organic solution (50% water, 20% ethanol, 30% propylene glycol) of compound II (methansulfonate acid addition salt).

The term "pharmaceutically acceptable organic solvent" as used herein refers to polypropylene glycol; polyethylene glycol (for example, polyethylene glycol 600, polyethylene glycol 900, polyethylene glycol 540, polyethylene glycol 1450, polyethylene glycol 6000, polyethylene glycol 8000 (all available from Union Carbide) and the like); pharmaceutically acceptabie alcohols which are liquids at about room temperature, approximately 20°C, (for example, propylene glycol, ethanol, 2-(2-ethoxyethoxy)ethanol (Transcutol® , Gattefosse, Westwood, NJ 07675), benzyl alcohol, glycerol, polyethylene glycol 200, polyethylene glycol 300, polyethylene glycol 400 and the like); polyoxyethylene castor oil derivatives (for example, polyoxyethyleneglyceroltriricinoleate or polyoxyl 35 castor oil (Cremophor®EL, BASF Corp.), polyoxyethyleneglycerol oxystearate (Cremophor®RH 40 (polyethyleneglycol 40 hydrogenated castor oil) or

Cremophor®RH 60 (polyethyleneglycol 60 hydrogenated castor oil), BASF Corp.) and the like); saturated polyglycolized glycerides (for example, Gelucire® 35/10, Gelucire® 44/14, Gelucire® 46/07, Gelucire® 50/13 or Gelucire® 53/10 and the like, available from Gattefosse, Westwood, NJ 07675); polyoxyethylene alkyl ethers (for example, cetomacrogol 1000 and the like); polyoxyethylene stearates (for example, PEG-6 stearate, PEG-8 stearate, polyoxyl 40 stearate NF, polyoxyethyl 50 stearate NF, PEG-12 stearate, PEG-20 stearate, PEG-100 stearate, PEG-12 distearate, PEG-32 distearate, PEG-150 distearate and the like); ethyl oleate, isopropyl palmitate, isopropyl myristate and the like; N-methylpyrrolidinone; parafin; cholesterol; lecithin; suppository bases; pharmaceutically acceptable waxes (for example, carnauba wax, yellow wax, white wax, microcrystalline wax, emulsifying wax and the like); pharmaceutically acceptable silicon fluids; soribitan fatty acid esters (including sorbitan laurate, sorbitan oleate, sorbitan palmitate, sorbitan stearate and the like); pharmaceutically acceptable saturated fats or pharmaceutically acceptable saturated oils (for example, hydrogenated castor oil (glyceryl-tris-12-hydroxystearate), cetyl esters wax (a mixture of primarily C14-C18 saturated esters of C14-C18 saturated fatty acids having a melting range of about 43-47°C), glyceryl monostearate and the like); and the like.

Pharmaceutically acceptable solvents also include pharmaceutically acceptable oils such as mineral oil or a vegetable oil (for example, safflower oil, peanut oil, olive oil, fractionated coconut oil (for example, mixed triglycerides with caprylic acid and capric acid (Miglyol® 812, available from Huls AG, Witten, Germany) and the like), propyleneglycol monolaurate and the like.

Saturated polyglycolized glycerides are described in the French Pharmacopeia 10th Edition. In particular, saturated polyglycolized glycerides are mixtures of mono-, di- and tri-glycerides and polyethylene glycol mono- and di-esters obtained either by partial alcoholysis of hydrogenated vegetable oils using polyethylene glycol of relative molecular weight ranging from 200 - 2000, or by esterification of saturated fatty acids using polyethylene glycol of relative molecular weight ranging from 200 - 2000 and glycerol. Each saturated polyglycolized glyceride is characterized by its nominal drop point, its nominal hydroxyl and saponification values and its nominal composition in fatty acids. The free glycerol content is less than 1%.

Cremophor®RH 60 (polyethyleneglycol 60 hydrogenated castor oil), BASF Corp.) and the like); saturated polyglycolized glycerides (for example, Gelucire® 35/10, Gelucire® 44/14, Gelucire® 46/07, Gelucire® 50/13 or Gelucire® 53/10 and the like, available from Gattefosse, Westwood, NJ 07675); polyoxyethylene alkyl ethers (for example, cetomacrogol 1000 and the like); polyoxyethylene stearates (for example, PEG-6 stearate, PEG-8 stearate, polyoxyl 40 stearate NF, polyoxyethyl 50 stearate NF, PEG-12 stearate, PEG-20 stearate, PEG-100 stearate, PEG-12 distearate, PEG-32 distearate, PEG-150 distearate and the like); ethyl oleate, isopropyl palmitate, isopropyl myristate and the like; N-methylpyrrolidinone; parafin; cholesterol; lecithin; suppository bases; pharmaceutically acceptable waxes (for example, carnauba wax, yellow wax, white wax, microcrystalline wax, emulsifying wax and the like); pharmaceutically acceptable silicon fluids; soribitan fatty acid esters (including sorbitan laurate, sorbitan oleate, sorbitan palmitate, sorbitan stearate and the like); pharmaceutically acceptable saturated fats or pharmaceutically acceptable saturated oils (for example, hydrogenated castor oil (glyceryl-tris-12-hydroxystearate), cetyl esters wax (a mixture of primarily C14-C18 saturated esters of C14-C18 saturated fatty acids having a melting range of about 43-47°C), glyceryl monostearate and the like); and the like.

Pharmaceutically acceptable solvents also include pharmaceutically acceptable oils such as mineral oil or a vegetable oil (for example, safflower oil, peanut oil, olive oil, fractionated coconut oil (for example, mixed triglycerides with caprylic acid and capric acid (Miglyol® 812, available from Huls AG, Witten, Germany) and the like), propyleneglycol monolaurate and the like.

Saturated polyglycolized glycerides are described in the French Pharmacopeia 10th Edition. In particular, saturated polyglycolized glycerides are mixtures of mono-, di- and tri-glycerides and polyethylene glycol mono- and di-esters obtained either by partial alcoholysis of hydrogenated vegetable oils using polyethylene glycol of relative molecular weight ranging from 200 - 2000, or by esterification of saturated fatty acids using polyethylene glycol of relative molecular weight ranging from 200 - 2000 and glycerol. Each saturated polyglycolized glyceride is characterized by its nominal drop point, its nominal hydroxyl and saponification values and its nominal composition in fatty acids. The free glycerol content is less than 1%.

Cremophor®RH 60 (polyethyleneglycol 60 hydrogenated castor oil), BASF Corp.) and the like); saturated polyglycolized glycerides (for example, Gelucire® 35/10, Gelucire® 44/14, Gelucire® 46/07, Gelucire® 50/13 or Gelucire® 53/10 and the like, available from Gattefosse, Westwood, NJ 07675); polyoxyethylene alkyl ethers (for example, cetomacrogol 1000 and the like); polyoxyethylene stearates (for example, PEG-6 stearate, PEG-8 stearate, polyoxyl 40 stearate NF, polyoxyethyl 50 stearate NF, PEG-12 stearate, PEG-20 stearate, PEG-100 stearate, PEG-12 distearate, PEG-32 distearate, PEG-150 distearate and the like); ethyl oleate, isopropyl palmitate, isopropyl myristate and the like; N-methylpyrrolidinone; parafin; cholesterol; lecithin; suppository bases; pharmaceutically acceptable waxes (for example, carnauba wax, yellow wax, white wax, microcrystalline wax, emulsifying wax and the like); pharmaceutically acceptable silicon fluids; soribitan fatty acid esters (including sorbitan laurate, sorbitan oleate, sorbitan palmitate, sorbitan stearate and the like); pharmaceutically acceptable saturated fats or pharmaceutically acceptable saturated oils (for example, hydrogenated castor oil (glyceryl-tris-12-hydroxystearate), cetyl esters wax (a mixture of primarily C14-C18 saturated esters of C14-C18 saturated fatty acids having a melting range of about 43-47°C), glyceryl monostearate and the like); and the like.

Pharmaceutically acceptable solvents also include pharmaceutically acceptable oils such as mineral oil or a vegetable oil (for example, safflower oil, peanut oil, olive oil, fractionated coconut oil (for example, mixed triglycerides with caprylic acid and capric acid (Miglyol® 812, available from Huls AG, Witten, Germany) and the like), propyleneglycol monolaurate and the like.

Saturated polyglycolized glycerides are described in the French Pharmacopeia 10th Edition. In particular, saturated polyglycolized glycerides are mixtures of mono-, di- and tri-glycerides and polyethylene glycol mono- and di-esters obtained either by partial alcoholysis of hydrogenated vegetable oils using polyethylene glycol of relative molecular weight ranging from 200 - 2000, or by esterification of saturated fatty acids using polyethylene glycol of relative molecular weight ranging from 200 - 2000 and glycerol. Each saturated polyglycolized glyceride is characterized by its nominal drop point, its nominal hydroxyl and saponification values and its nominal composition in fatty acids. The free glycerol content is less than 1%.

More particularly, the preferred saturated polyglycolized glycerides are characterized as follows.

Gelucire® 35/10
drop point: 29-34°C (preferably, 31.2°C)
hydroxyl value: 70-90 mg KOH/g (preferably, 74 mg KOH/g)
saponification value: 120-134 mg KOH/g (preferably, 134 mg KOH/g)

fatty acid composition:
caprylic acid (C8): 1-7% (preferably, 2.1%)
capric acid (C10): 1-7% (preferably, 2.2%)
lauric acid (C12): 31-41% (preferably, 35.4%)
myristic acid (C14): 7-17% (preferably, 12.9%)
palmitic acid (C16): 12-22% (preferably, 20.7%)
stearic acid (C18): 23-33% (preferably, 26.2%)

Gelucire® 44/14
drop point: 42.5-47.5°C
hydroxyl value: 30-50 mg KOH/g
saponification value: 76-90 mg KOH/g

fatty acid composition:
caprylic acid (C8): 4-10%
capric acid (C10): 3-9%
lauric acid (C12): 40-50%
myristic acid (C14): 14-24%
palmitic acid (C16): 4-14%
stearic acid (C18): 5-15%

Gelucire® 46/07

drop point: 47-52°C (preferably, 49.3°C)
hydroxyl value: 65-85 mg KOH/g (preferably, 70 mg KOH/g)
saponification value: 126-140 mg KOH/g (preferably, 139 mg KOH/g)

fatty acid composition:
caprylic acid (C8): < 3% (preferably, < 0.1%)
capric acid (C10): < 3% (preferably, < 0.1%)
lauric acid (C12): < 5% (preferably, 0.9%)
myristic acid (C14): < 5% (preferably, 1.4%)
palmitic acid (C16): 40-50% (preferably, 44%)
stearic acid (C18): 48-58% (preferably, 52.8%)

Gelucire® 50/13

drop point: 46-51°C (preferably, 48.7°C)
hydroxyl value: 36-56 mg KOH/g (preferably, 52 mg KOH/g)
saponification value: 67-81 mg KOH/g (preferably, 74 mg KOH/g)

fatty acid composition:
caprylic acid (C8): < 3% (preferably, 0.2%)
capric acid (C10): < 3% (preferably, 0.2%)
lauric acid (C12): < 5% (preferably, 2.2%)
myristic acid (C14): < 5% (preferably, 1.8%)
palmitic acid (C16): 40-50% (preferably, 42.5%)
stearic acid (C18): 48-58% (preferably, 52.6%)

Gelucire® 53/10

drop point: 49-54°C (preferably, 52.5°C)
hydroxyl value: 25-45 mg KOH/g (preferably, 35 mg KOH/g)
saponification value: 98-112 mg KOH/g (preferably, 104 mg KOH/g)

fatty acid composition:
caprylic acid (C8): < 3% (preferably, < 0.1%)
capric acid (C10): < 3% (preferably, < 0.1%)
lauric acid (C12): < 5% (preferably, 0.4%)
myristic acid (C14): < 5% (preferably, 1.0%)
palmitic acid (C16): 40-50% (preferably, 43%)
stearic acid (C18): 48-58% (preferably, 54.2%)

The term "pharmaceutically acceptable acid" as used herein refers to (i) an inorganic acid such as hydrochloric acid, hydrobromic acid, hydroiodic acid and the like, (ii) an organic mono-, di- or tri-carboxylic acid (for example, formic acid, acetic acid, adipic acid, alginic acid, citric acid, ascorbic acid, aspartic acid, benzoic acid, butyric acid, camphoric acid, gluconic acid, glucuronic acid, galactaronic acid, glutamic acid, heptanoic acid, hexanoic acid, fumaric acid, lactic acid, lactobionic acid, malonic acid, maleic acid, nicotinic acid, oxalic acid, pamoic acid, pectinic acid, 3-phenylpropionic acid, picric acid, pivalic acid, propionic acid, succinic acid, tartaric acid, undecanoic acid and the like) or (iii) a sulfonic acid (for example, benzenesulfonic acid, sodium bisulfate, sulfuric acid, camphorsulfonic acid, dodecylsulfonic acid, ethanesulfonic acid, methanesulfonic acid, isethionic acid, naphthalenesulfonic acid, p-toluenesulfonic acid and the like).

The term "pharmaceutically acceptable surfactant" as used herein refers to a pharmaceutically acceptable non-ionic surfactant (for example, polyoxyethylenepolypropylene glycol, such as Poloxamer®68 (BASF Wyandotte Corp.) or a mono fatty acid ester of polyoxyethylene (20) sorbitan (for example, polyoxyethylene (20) sorbitan monooleate (Tween® 80), polyoxyethylene (20) sorbitan monostearate (Tween® 60), polyoxyethylene (20) sorbitan monopalmitate (Tween® 40), polyoxyethylene (20) sorbitan monolaurate (Tween® 20) and the like) and the like) or a pharmaceutically acceptable anionic surfactant (for example, sodium lauryl sulfate and the like).

The term "solution" as used herein refers to solutions of the pharmaceutically active agent dissolved in the pharmaceutically acceptable solvent or mixture of solvents wherein the solution remains in liquid form at about

room temperature; or it refers to semi-solid solutions wherein the pharmaceutically active agent is dissolved in a pharmaceutically acceptable solvent or mixture of solvents which is a liquid at temperatures above about room temperature (particularly, at about the temperature of the human body) but is a solid or semi-solid at about room temperature.

A preferred composition of the invention comprises a solution of (1) an HIV protease inhibiting compound (preferably, a compound of the formula II); and (2) a pharmaceutically acceptable acid or a mixture of pharmaceutically acceptable acids in a pharmaceutically acceptable organic solvent or a mixture of pharmaceutically acceptable organic solvents, the solvent comprising a pharmaceutically acceptable alcohol.

Another preferred composition of the invention comprises a solution of (1) a compound of the formula II in the amount of from about 2% to about 30% (preferably, from about 4% to about 30%) by weight of the total solution; and (2) a total of from about 0.2 molar equivalent to about 3 molar equivalents (based on compound II) of (i) a pharmaceutically acceptable acid or (ii) a mixture of pharmaceutically acceptable acids in a pharmaceutically acceptable organic solvent or a mixture of pharmaceutically acceptable organic solvents, the solvent comprising a pharmaceutically acceptable alcohol.

Yet another preferred composition of the invention comprises a solution of (1) an HIV protease inhibiting compound (preferably, a compound of the formula II); and

(2) a pharmaceutically acceptable acid or a mixture of pharmaceutically acceptable acids in a pharmaceutically acceptable organic solvent or a mixture of pharmaceutically acceptable organic solvents, the solvent comprising a pharmaceutically acceptable alcohol, wherein the solution is encapsulated in a soft elastic gelatin capsule (SEC) or a hard gelatin capsule.

Yet another preferred composition of the invention comprises a solution of (1) a compound of the formula II in the amount of from about 2% to about 30% (preferably, from about 4% to about 30%) by weight of the total solution; and (2) a total of from about 0.2 molar equivalent to about 3 molar equivalents (based on compound II) of (i) a pharmaceutically acceptable acid or (ii) a mixture of pharmaceutically acceptable acids in a pharmaceutically acceptable organic solvent or a mixture of pharmaceutically acceptable organic solvents, the solvent

comprising a pharmaceutically acceptable alcohol, wherein the solution is encapsulated in a soft elastic gelatin capsule (SEC) or a hard gelatin capsule.

Preferably, the pharmaceutically acceptable organic solvent or mixture of pharmaceutically acceptable organic solvents comprises from about 50% to about 95% by weight of the total solution. More preferably, the pharmaceutically acceptable organic solvent or mixture of pharmaceutically acceptable organic solvents comprises from about 70% to about 95% by weight of the total solution.

Preferred pharmaceutically acceptable alcohols include propylene glycol, polyethylene glycol and ethanol.

A preferred pharmaceutically acceptable solvent is propylene glycol or a mixture of propylene glycol (about 80% v/v) and ethanol (about 20% v/v) or a mixuture of propylene glycol (from about 80% to about 90% v/v), ethanol (from about 5% to about 10% v/v) and water (from about 5% to about 10% v/v).

Another preferred pharmaceutically acceptable solvent is (i) polyethylene glycol (most preferably, polyethylene glycol 540, polyethylene glycol 900, polyethylene glycol 600 or polyethylene glycol 400) or (ii) a mixture of polyethylene glycols (for example, polyethylene glycol 900 (about 40% by weight of the total solution) and polyethylene glycol 300 (about 40% by weight of the total solution)) or (iii) a mixture of polyethylene glycol (about 80% by weight of the total solution) and propylene glycol (from about 5% to about 12% by weight of the total solution) or (iv) a mixture of polyethylene glycol (about 70% by weight of the total solution), propylene glycol (about 4% by weight of the total solution) and ethanol (about 4% by weight of the total solution) or (v) a mixture of polyethylene glycol and a polyoxyethylene castor oil derivative (for example, a mixture of polyethylene glycol 600 (about 32% by weight of the total solution) and polyoxyethyleneglycerol triricinoleate (about 42% by weight of the total solution)).

A preferred pharmaceutically acceptable acid is hydrochloric acid, citric acid or p-toluenesulfonic acid or a mixture of two of these acids.

A more preferred composition of the invention comprises a solution of:
(1) a compound of the formula II in the amount of from about 2% to about 30% (preferably, from about 4% to about 30%) by weight of the total solution; and
(2) a total of from about 0.2 to about 2 molar equivalents (based on compound II) of (i) a pharmaceutically acceptable acid or (ii) a mixture of pharmaceutically

acceptable acids in a pharmaceutically acceptable organic solvent or a mixture of pharmaceutically acceptable organic solvents, the solvent comprising a pharmaceutically acceptable alcohol, wherein the solution is encapsulated in a soft elastic capsule or a hard gelatin capsule.

In the more preferred composition of the invention, the preferred pharmaceutically acceptable solvents and acids are as described above for the preferred composition of the invention.

A most preferred composition of the invention comprises a solution of (1) a compound of the formula **III** in the amount of from about 2% to about 30% (preferably, from about 4% to about 30%) by weight of the total solution; and (2) a total of from about 0.2 to about 2 molar equivalents (based on compound **III**) of (i) a pharmaceutically acceptable acid or (ii) a mixture of pharmaceutically acceptable acids in a pharmaceutically acceptable organic solvent or a mixture of pharmaceutically acceptable organic solvents, the solvent comprising a pharmaceutically acceptable alcohol, wherein the solution is encapsulated in a soft elastic capsule or a hard gelatin capsule.

In the most preferred composition of the invention, the preferred pharmaceutically acceptable solvents and acids are as described above for the preferred composition of the invention.

An even more preferred composition of the invention comprises a solution of (1) a compound of the formula **III** in the amount of from about 2% to about 30% by weight of the total solution (preferably, from about 15% to about 25% by weight of the total solution) and (2) a total of from about 0.2 to about 2 molar equivalents (based on compound **III**) of (i) a pharmaceutically acceptable acid or (ii) a mixture of pharmaceutically acceptable acids in a pharmaceutically acceptable organic solvent comprising a mixture of (a) a pharmaceutically acceptable alcohol or mixture of pharmaceutically acceptable alcohols in a total amount of from about 2% to about 50% by weight of the total solution, said alcohol or mixture of alcohols being a liquid at room temperature and (b) a pharmaceutically acceptable organic solvent or a mixture of pharmaceutically

acceptable organic solvents in a total amount of from about 20% to about 60% by weight of the total solution, said solvent or mixture of solvents having a melting point between about 20°C and about 60°C (preferably, between about 20°C and about 50°C), said solvent or mixture of solvents being miscible with the alcohol or mixture of alcohols and providing a homogeneous mixture with the alcohol or mixture of alcohols, said homogeneous mixture being a solid or semi-solid at about 20°C, wherein the solution is encapsulated in a soft elastic capsule or a hard gelatin capsule.

An even more preferred composition of the invention comprises a solution of (1) a compound of the formula **III** in the amount of from about 2% to about 30% by weight of the total solution (preferably, from about 15% to about 25% by weight of the total solution) and (2) a total of from about 0.2 to about 2 molar equivalents (based on compound **III**) of (i) a pharmaceutically acceptable acid or (ii) a mixture of pharmaceutically acceptable acids in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of from about 5% to about 40% by weight of the total solution, (b) ethanol in the amount of from about 2% to about 20% (preferably, from about 2% to about 8% by weight of the total solution and, more preferably, from about 5% to about 6% by weight of the total solution), and (c) polyethylene glycol 540 in the amount of from about 20% to about 60% (preferably, from about 30% to about 40% by weight of the total solution) or a total amount of from about 20% to about 60% by weight of the total solution (preferably, from about 25% to about 40% by weight of the total solution and, more preferably, from about 30% to about 40% by weight of the total solution) of (i) a saturated polyglycolized glyceride ((in particular, Gelucire® 35/10, Gelucire® 44/14, Gelucire® 46/07, Gelucire® 50/13 or Gelucire® 53/10 and the like) or (ii) a mixture of saturated polyglycolized glycerides, wherein the solution is encapsulated in a soft elastic capsule or a hard gelatin capsule.

In the even more preferred composition of the invention, if the composition comprises from about 2% to about 20% by weight of the total solution of compound **III**, it is not necessary for the composition to comprise a pharmaceutically acceptable acid.

A most highly preferred composition of the invention comprises a solution of (1) a compound of the formula III in the amount of from about 20% to about 25% by weight of the total solution and (2) a total of from about 1.5 to about 2 molar equivalents (based on compound III) of hydrochloric acid in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of from about 20 % to about 22% by weight of the total solution, (b) ethanol in the amount of from about 5% to about 6% by weight of the total solution, and
(c) saturated polyglycolized glyceride (in particular, Gelucire® 44/14 or Gelucire® 35/10) in the amount of from about 30% to about 35% by weight of the total solution, wherein the solution is encapsulated in a hard gelatin capsule.

Another most highly preferred composition of the invention comprises a solution of (1) a compound of the formula III in the amount of from about 15% to about 20% by weight of the total solution and (2) a total of from about 0.3 to about 0.6 molar equivalents (based on compound III) of hydrochloric acid in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of about 12% by weight of the total solution, (b) ethanol in the amount of from about 5% to about 6% by weight of the total solution, and (c) saturated polyglycolized glyceride (in particular, Gelucire® 44/14 or Gelucire® 50/13) in the amount of from about 30% to about 35% by weight of the total solution, wherein the solution is encapsulated in a hard gelatin capsule.

Another most highly preferred composition of the invention comprises a solution of (1) a compound of the formula III in the amount of from about 15% to about 20% by weight of the total solution and (2) a total of from about 0.3 to about 0.6 molar equivalents (based on compound III) of hydrochloric acid in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of about 12% by weight of the total solution, (b) ethanol in the amount of from about 10% to about 15% by weight of the total solution, and (c) saturated polyglycolized glyceride (in particular, Gelucire® 44/14 or Gelucire® 50/13) in the amount of from about 30% to about 35% by weight of the total solution, wherein the solution is encapsulated in a hard gelatin capsule.

Another most highly preferred composition of the invention comprises a solution of (1) a compound of the formula III in the amount of from about 10% to about 15% by weight of the total solution and (2) a total of from about 0.3 to about 0.6 molar equivalents (based on compound III) of hydrochloric acid in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of about 15% by weight of the total solution, (b) ethanol in the amount of from about 10% to about 15% by weight of the total solution, and (c) saturated polyglycolized glyceride (in particular, Gelucire® 44/14 or Gelucire® 50/13) in the amount of from about 30% to about 35% by weight of the total solution, wherein the solution is encapsulated in a hard gelatin capsule.

Another most highly preferred composition of the invention comprises a solution of (1) a compound of the formula III in the amount of from about 15% to about 20% by weight of the total solution and (2) a total of from about 0.3 to about 0.8 molar equivalents (based on compound III) of hydrochloric acid in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of from about 13% to about 14% by weight of the total solution, (b) ethanol in the amount of about 14% by weight of the total solution, and (c) saturated polyglycolized glyceride (in particular, Gelucire® 44/14 or Gelucire® 50/13) in the amount of from about 30% to about 35% by weight of the total solution, wherein the solution is encapsulated in a hard gelatin capsule.

Another most highly preferred composition of the invention comprises a solution of (1) a compound of the formula III in the amount of from about 15% to about 20% by weight of the total solution in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of about 40% by weight of the total solution, (b) ethanol in the amount of about 2% to about 3% by weight of the total solution, and (c) polyethylene glycol 540 in the amount of from about 30% to about 35% by weight of the total solution, wherein the solution is encapsulated in a hard gelatin capsule.

Another embodiment of the present invention comprises a solid pharmaceutical composition comprising a mixture of (A) a solution of (1) an HIV protease inhibiting compound (preferably, a compound of the formula III) in the amount of from about 4% to about 30% by weight of the total solution (preferably, from about 15% to about 25% by weight of the total solution) and (2) a total of from about 0.2 to about 2 molar equivalents (based on the HIV protease inhibiting compound) of (i) a pharmaceutically acceptable acid or (ii) a mixture of pharmaceutically acceptable acids in a pharmaceutically acceptable organic solvent comprising a mixture of (a) a pharmaceutically acceptable alcohol or mixture of pharmaceutically acceptable alcohols in a total amount of from about 2% to about 50% by weight of the total solution, said alcohol or mixture of alcohols being a liquid at about room temperature and (b) a pharmaceutically acceptable solvent or a mixture of pharmaceutically acceptable solvents in a total amount of from about 20% to about 60% by weight of the total solution, said solvent or mixture of solvents having a melting point between about 20°C and about 60°C (perferably, between about 20°C and about 50°C), said solvent or mixture of solvents being miscible with the alcohol or mixture of alcohols and providing a homogeneous mixture with the alcohol or mixture of alcohols, said homogeneous mixture being a solid or semi-solid at about 20°C and (B) a pharmaceutically acceptable granulating agent or a mixture of pharmaceutically acceptable granulating agents. A more preferred embodiment comprises the above-mentioned solid composition as a granulation which is encapsulated in a hard gelatin capsule for administration.

An even more preferred embodiment of the solid composition comprises a solid pharmaceutical composition comprising a mixture of (A) a solution of (1) a compound of the formula III in the amount of from about 4% to about 30% by weight of the total solution (preferably, from about 15% to about 25% by weight of the total solution) and (2) a total of from about 0.2 to about 2 molar equivalents (based on compound III) of (i) a pharmaceutically acceptable acid or (ii) a mixture of pharmaceutically acceptable acids in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of from about 5% to about 40% by weight of the total solution, (b) ethanol in the amount of from about 2% to about 20% (preferably, from about 2% to about 8%

by weight of the total solution and, more preferably, from about 5% to about 6% by weight of the total solution), and (c) polyethylene glycol 540 in the amount of from about 20% to about 60% (preferably, from about 30% to about 40% by weight of the total solution) or a total amount of from about 20% to about 60% by weight of the total solution (preferably, from about 25% to about 40% by weight of the total solution and, more preferably, from about 30% to about 40% by weight of the total solution) of (i) a saturated polyglycolized glyceride ((in particular, Gelucire® 35/10, Gelucire® 44/14, Gelucire® 46/07, Gelucire® 50/13 or Gelucire® 53/10 and the like) or (ii) a mixture of saturated polyglycolized glycerides and (B) a pharmaceutically acceptable granulating agent or a mixture of pharmaceutically acceptable granulating agents. A most preferred embodiment comprises the above-mentioned solid composition as a granulation which is encapsulated in a hard gelatin capsule for administration.

The term "pharmaceutically acceptable granulating agent" as used herein refers to silicon dioxide, colloidal silicon dioxide (for example, Cab-o-sil®, available from Cabot Corp.), microcrystalline cellulose, starch, talc, calcium carbonate, pectin, aluminum silicate, maltodextrin, crospovidone (for example, Polyplasdone®XL or XL10, available from GAF Corp.) and the like.

Preferably, the pharmaceutically acceptable granulating agent or mixture of pharmaceutically acceptable granulating agents comprises from about 0.5 % to about 30 % by weight of the solid pharmaceutical composition.

The compounds of formula I and II contain two or more asymmetric carbon atoms and thus can exist as pure diastereomers, mixtures of diastereomers, diastereomeric racemates or mixtures of diastereomeric racemates. The present invention is intended to include within its scope all of the isomeric forms. The terms "R" and "S" configuration as used herein are as defined by IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, Pure Appl. Chem. (1976) 45, 13-30.

The preferred isomer of the compound of formula II is (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane (compound III).

The term "lower alkyl" as used herein refers to straight or branched chain alkyl radicals containing from 1 to 6 carbon atoms including, but not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, n-pentyl, 1-methylbutyl, 2,2-dimethylbutyl, 2-methylpentyl, 2,2-dimethylpropyl, n-hexyl and the like.

The composition and preparation of the soft elastic gelatin capsule itself is well known in the art. The composition of a soft elastic gelatin capsule typically comprises from about 30% to about 50% by weight of gelatin NF, from about 20% to about 30% by weight of a plasticizer and from about 25% to about 40% by weight of water. Plasticizers useful in the preparation of soft elastic gelatin capsules are glycerin, sorbitol or propylene glycol and the like; or combinations thereof. A preferred soft elastic gelatin capsule has a composition comprising gelatin NF (Type 195) (about 42.6% by weight), glycerin (USP) (about 96% active; about 13.2% by weight), purified water (USP) (about 27.4% by weight), sorbitol special (about 16% by weight) and titanium dioxide (USP) (about 0.4% by weight).

The soft elastic gelatin capsule material can also comprise additives such as preservatives, opacifiers, dyes or flavors and the like.

Various methods can be used for manufacturing and filling the soft elastic gelatin capsules, for example, a seamless capsule method, a rotary method (developed by Scherer) or a method using a Liner machine or an Accogel machine and the like. Also various manufacturing machines can be used for manufacturing the capsules.

Hard gelatin capsules are purchased from Capsugel, Greenwood, SC. Capsules are filled manually or by capsule filling machine. The target filling volume/weight depends on the potency of the filling solution in combination with the desired dosage strength.

In general, the compositions of this invention can be prepared in the following manner. The pharmaceutically acceptable organic solvent or mixture of solvents is mixed with any additives (for example, water, pharmaceutically acceptable oils, glycerin, pharmaceutically acceptable surfactants or antioxidants). To this mixture is added the pharmaceutically acceptable acid with stirring. To this mixture is added the HIV protease inhibiting compound (for

example, the compound of formula II) with stirring. Additional solvent is added until a clear solution is obtained and/or to reach the desired final volume of solution. The appropriate volume of final solution needed to provide the desired dose of the HIV protease inhibiting compound can be filled into hard gelatin capsules or soft elastic gelatin capsules.

In general, the even more preferred compositions of the invention can be prepared in the following manner. The pharmaceutically acceptable alcohol (other than ethanol) is mixed with any other additives such as surfactants. If ethanol is part of composition, the ethanol is added to this solution and stirred until the solution is clear to slightly cloudy. The pharmaceutically acceptable acid or mixture of acids is added and the solution is stirred until it is clear to slightly cloudy. The HIV protease inhibiting compound (for example, compound II) is added and the solution is stirred until it is clear or slightly cloudy. The other pharmaceutically acceptable solvent or mixture of solvents (for example, polyethylene glycol or saturated polyglycolized glyceride) is heated just enough to be liquified. The liquified solvent is added to the alcohol solution of the HIV protease inhibiting compound and stirred well. The appropriate volume of final solution needed to provide the desired dose of the HIV protease inhibiting compound can be filled into hard gelatin capsules or soft elastic gelatin capsules.

In general, the solid pharmaceutical composition of the invention can be prepared in the following manner. The pharmaceutically acceptable liquid alcoholic solvent(s) (other than ethanol) is mixed with any other additives, such as surfactants. If ethanol is one of the solvents, the ethanol is then added to the above mixture and stirred until the solution is clear to slightly cloudy. Then the pharmaceutically acceptable acid (or mixture of acids) is added and the mixture is stirred until it is clear to slightly cloudy. The HIV protease inhibiting compound (for example, compound II) is added and the mixture is stirred until it is clear to slightly cloudy. The other pharmaceutically acceptable solvent or mixture of solvents (for example, polyethylene glycol or saturated polyglycolized glyceride) is heated just enough to be liquified. The liquified solvent is added to the solution of the HIV protease inhibiting compound and stirred well. This solution

is added slowly with mixing to the granulating agent and mixed well until the mixture is a dry solid. The resulting solid is passed through an appropriately sized seive to obtain granules. The appropriate amount of the granulation to provide the desired dose is filled into hard gelatin capsules.

The following examples will serve to further illustrate the invention.

Example 1 (non-formulated capsule)

An amount of compound **III** (free base) equivalent to a 5 mg/kg dose was placed in hard gelatin capsules (gray, size 0). These capsules were administered to fasted dogs with 10 ml of water.

Example 2 (Capsule)

An amount of compound **III** (free base) equivalent to a 5 mg/kg dose was placed in hard gelatin capsules (gray, size 0). These capsules were administered to non-fasted dogs with ten milliliter of water.

Example 3 (Capsule)

An amount of the bis-tosylate salt of compound **III** equivalent to a 5 mg/kg dose of compound **III** (base equivalent) was filled into hard gelatin capsules (gray, size 0). These capsules were administered to fed dogs with ten milliliter of water.

Example 4 (Solution)

A 5 mg (free base equivalent)/ml solution of the base compound **III** in 20% ethanol: 30% propylene glycol: dextrose containing 2- molar equivalents of methane sulfonic acid.

Component	% By Weight
Compound **III** (free base)	0.5
Propylene glycol (Aldrich, reagent)	31.9
Ethanol (USP, 200 proof)	16.2
methanesulfonic acid (Aldrich reagent)	0.14
Dextrose	3.6
Water for injection (USP)	47.6

Example 5 (SEC)

A 100 mg/ml solution of the base compound **III** in 20% ethanol: 80% polyethylene glycol-400 encapsulated in SEC.

Component	% By Weight
Compound **III** (free base)	8.6
Polyethylene glycol 400 (USP)	77.8
Ethanol (USP, 200 proof)	13.5

Example 6 (SEC)

A 100 mg/ml solution of the base compound **III** in 20% ethanol: 80% propylene glycol with 50 mg/ml p-toluene sulfonic acid, encapsulated in SEC.

Component	% By Weight
Compound **III** (free base)	8.8
Propylene glycol (NF)	73.0
Ethanol (USP, 200 proof)	13.8
p-toluenesulfonic acid (Sigma, reagent)	4.4

Example 7 (SEC)

A 100 mg/ml solution of the base compound **III** in 20% ethanol: 80% propylene glycol encapsulated in SEC.

Component	% By Weight
Compound **III** (free base)	9.2
Propylene glycol 400 (NF)	76.3
Ethanol (USP, 200 proof)	14.5

Example 8 (SEC)

A 100 mg/ml solution of the base compound **III** in 98% propylene glycol, 2% glycerin with 50.0 mg/ml p-toluene sulfonic acid encapsulated in SEC.

Component	% By Weight
Compound **III** (free base)	8.4
Propylene glycol (NF)	85.6
Glycerin (USP, 96 %)	1.38
p-toluenesulfonic acid (Sigma, reagent)	4.2

Example 9 (capsule)

Component	% By Weight
Compound III (free base)	10.0
Polyethylene Glycol 540	74.5
Propylene glycol	10.0
p-toluene sulfonic acid, monohydrate, Sigma	5.5

Example 10 (solution)

A 45 mg/ml solution of the base compound III in 9% ethanol, 9% water, 82% propylene glycol with 24.0 mg/ml p-toluene sulfonic acid and 45 mg/ml aspartame.

Component	% By Weight
Compound III (free base)	4.0
Propylene glycol (NF)	75.5
Ethanol (USP, 200 proof)	6.3
p-toluenesulfonic acid (Sigma, reagent)	2.1
Water for injection (USP)	8.0
Aspartame	4.0

Example 11 (capsule)

Component	% By Weight
Compound III (free base)	17.0
Polyethylene Glycol 540	68.1
Propylene glycol	4.3
Ethanol	4.3
Glycerin	1.7
p-toluene sulfonic acid, monohydrate, Sigma	4.7

Example 12 (capsule)

Component	% By Weight
Compound III (free base)	10.0
Polyethylene Glycol 540	80.0
Propylene glycol	5.0
p-toluene sulfonic acid, monohydrate, Sigma	5.1

Example 13 (capsule)

Component	% By Weight
Compound III (free base)	5.0
Polyethylene Glycol 300	80.0
Propylene glycol	12.3
p-toluene sulfonic acid, monohydrate, Sigma	2.8

Example 14 (capsule)

Component	% By Weight
Compound III (free base)	10.0
Polyethylene Glycol 900	42.3
Polyethylene Glycol 300	42.2
p-toluene sulfonic acid, monohydrate, Sigma	5.5

Example 15 (capsule)

Component	% By Weight
Compound III (free base)	10.0
Polyethylene Glycol 540	84.5
p-toluene sulfonic acid, monohydrate, Sigma	5.5

Example 16 (capsule)

Component	% By Weight
Compound III (free base)	12.5
Polyethylene Glycol 540	80.6
p-toluene sulfonic acid, monohydrate, Sigma	6.9

Example 17 (capsule)

A 100 mg/ml solution of the base compound **III** in 90% propylene glycol, 5% ethanol, 5% water with 2 molar equivalents of hydrochloric acid encapsulated in hard gelatin capsule.

Component	% By Weight
Compound **III** (free base)	8.8
Propylene glycol (NF)	82.3
Ethanol (USP, 200 proof)	3.5
Hydrochloric acid (reagent)	0.9
Water for injection (USP)	4.4

To propylene glycol (700 mL) was added ethanol (50 mL, 200 proof) with stirring. Water for injection (13.7 mL) was added with stirring, followed by the addition with stirring of hydrochloric acid (46.7 mL, 554.8 mmol). To this mixture was added compound **III** (200 g, 277.4 mmol). Stirring was continued until a clear solution was obtained. Propylene glycol was then added to give a total volume of one liter. The appropriate volume of this solution was filled into hard gelatin capsules.

Example 18 (capsule)

Component	% By Weight
Compound **III** (free base)	21.0
Polyethylene Glycol 600	31.6
Hydrochloric acid, reagent	5.3
Cremophor® EL	42.1

Example 19 (SEC)

Component	% By Weight
Compound **III** (free base)	20.1
Polyethylene glycol 600 (USP)	68.4
Hydrochloric acid (reagent)	4.6
Water for injection (USP)	1.6
Ascorbic acid (USP)	1.25
Gylcerin (USP, 96 %)	4.0

In an appropriately sized container, was mixed 36.8 mL of concentrated hydrochloric acid, water for injection (12.5 mL), glycerin (32 g), ascorbic acid (10 g) and polyethylene glycol 600 (540 mL). The mixture was stirred until a homogeneous solution was obtained. To this solution was slowly added compound **III** (160 g, 221 mmol) with continuous stirring until a clear solution was obtained. This solution was transferred to an appropriate container and the head space was purged with nitrogen. The appropriate volume of this solution was filled into soft elastic gleatin capsules.

Example 20 (SEC)

Component	% By Weight
Compound **III** (free base)	16.0
Propylene Glycol (NF)	10.0
Citric acid (anhydrous)	16.0
Cremophor® EL	33.0
Ethanol (USP, 200 proof)	5.0
Tween® 80 (USP)	20.0

Propylene glycol (1.0 g) and citric acid (1.6 g) were mixed with stirring. To this mixture was added Tween® 80 (2.0 g) with stirring. Compound **III** (1.6 g, 2.22 mmol) was added, making a thick white paste. To this mixture was added ethanol (0.5 g) and Cremophore® EL (3.3 g). After mixing well, a clear solution was obtained. Sonication was used to help remove trapped air bubbles from the solution. The appropriate volume of this solution was filled into soft elastic gelatin capsules.

Example 21 (capsule)

Component	% By Weight
Compound **III** (free base)	2.0
Propylene Glycol (NF)	2.64
Ethanol (USP, 200 proof)	5.36
Polyethylene glycol 540	90.0

Example 22 (capsule)

Component	% By Weight
Compound III (free base)	22.12
Propylene Glycol (NF)	29.5
p-toluenesulfonic acid, monohydrate, Sigma	5.8
Cremophor® RH40	3.7
Ethanol (USP, 200 proof)	5.50
Polyethylene glycol 540	33.3

Example 23 (capsule)

Component	% By Weight
Compound III (free base)	22.12
Propylene Glycol (NF)	29.5
p-toluenesulfonic acid, monohydrate, Sigma	5.8
Cremophor® RH40	3.7
Ethanol (USP, 200 proof)	5.50
Gelucire® 44/14	33.3

Example 24 (capsule)

Component	% By Weight
Compound III (free base)	15.01
Propylene Glycol (NF)	40.06
p-toluenesulfonic acid, monohydrate, Sigma	3.97
Tween® 80	5.05
Ethanol (USP, 200 proof)	2.52
Polyethylene glycol 540	33.4

Propylene glycol and polysorbate 80 were mixed until the solution was clear to slightly cloudy. Ethanol was added and the solution was stirred until the solution was clear or slightly cloudy. p-Toluenesulfonic acid was added to the solution and stirred until the solution was clear or slightly cloudy. Compound III was added to the solution and stirred until the solution was clear or slightly cloudy. Polyethylene glycol 540 was heated to not more than 45°C until it was in the liquid state. The heated polyethylene glycol 540 was then added to the

solution of compound III and the mixture was stirred well. The appropriate volume of this final mixture to provide the desired dose of compound III was filled into hard gelatin capsules.

Example 25 (capsule)

Component	% By Weight
Compound III (free base)	21.95
Propylene Glycol (NF)	25.64
hydrochloric acid, reagent	5.85
Cremophor® RH40	3.76
Ethanol (USP, 200 proof)	5.48
Gelucire® 44/14	33.3
Miglyol®812	3.98

Example 26 (capsule)

Component	% By Weight
Compound III (free base)	22.1
Propylene Glycol (NF)	25.75
hydrochloric acid, reagent	5.9
Ethanol (USP, 200 proof)	5.56
Gelucire® 44/14	33.29
Miglyol® 812	3.73
Tween® 80	3.66

Example 27 (capsule)

Component	% By Weight
Compound III (free base)	21.78
Propylene Glycol (NF)	19.91
Hydrochloric acid, reagent	5.96
Cremophor® RH40	6.82
Ethanol (USP, 200 proof)	5.51
Gelucire® 44/14	33.28
Miglyol® 812	6.73

Example 28 (capsule)

Component	% By Weight
Compound III (free base)	18.03
Propylene Glycol (NF)	12.36
Citric acid (USP, anhydrous, powder)	4.12
Hydrochloric acid, reagent	1.83
Cremophor® EL	17.51
Ethanol (USP, 200 proof)	5.10
Tween® 80 (USP)	5.10
Gelucire® 44/14	33.38
Miglyol®	2.58

Example 29 (SEC)

Component	% By Weight
Compound III (free base)	16.0
Propylene glycol (USP)	10.0
Ethanol (USP, 200 proof, dehydrated)	5.0
Cremophor® EL (polyoxyl 35, castor oil, NF)	33.0
Citric acid (USP, anhydrous, powder)	16.0
Tween® 80	20.0

Example 30 (capsule)

Component	% By Weight
Compound III (free base)	14.99
Propylene Glycol (NF)	40.03
Hydrochloric acid, reagent	4.50
Tween® 80	5.10
Ethanol (USP, 200 proof)	2.55
Polyethylene glycol 540	32.83

Propylene glycol and Tween® 80 (USP) were mixed until the solution was clear to slightly cloudy. Ethanol was added and the solution was stirred until the solution was clear or slightly cloudy. Hydrochloric acid was added to the solution and stirred until the solution was clear or slightly cloudy. Compound III was

added to the solution and stirred until the solution was clear or slightly cloudy. Polyethylene glycol 540 was heated to not more than 45°C until it was in the liquid state. The heated polyethylene glycol 540 was then added to the solution of compound III and the mixture was stirred well. The appropriate volume of this final mixture to provide the desired dose of compound III was filled into hard gelatin capsules.

Example 31 V93-464 (capsule)

Component	% By Weight
Compound III (free base)	22.12
Propylene Glycol (NF)	29.5
p-toluenesulfonic acid, monohydrate, Sigma	5.8
Cremophor® RH40	3.7
Ethanol (USP, 200 proof)	5.5
Polyethylene glycol 540	33.3

Step 1. The compound of formula III was dissolved in the ethanol with mixing. The propylene glycol was added and mixing was continued until a homogeneous solution was obtained. All of the remaining ingredients (except the acid and the polyethylene glycol) were added and mixing was continued until a homogeneous solution was obtained. The acid was then added with mixing.

Step 2. The polyethylene glycol was warmed (to not more than 45°C) until it was liquified. The liquified polyethylene glycol was then added with mixing to the solution resulting from Step 1. The appropriate volume of this final mixture to provide the desired dose of compound III was filled into hard gelatin capsules.

Example 32 (capsule)

Component	% By Weight
Compound III (free base)	22.12
Propylene Glycol (NF)	29.5
p-toluenesulfonic acid, monohydrate, Sigma	5.8
Cremophor® RH40	3.7
Ethanol (USP, 200 proof)	5.5
Gelucire® 44/14	33.3

This composition was prepared according to the process of Example 31 with the exception that the polyethylene glycol was replaced by Gelucire® 44/14 (which was warmed to no more than 10°C above its melting point).

Example 33 (capsule)

Component	% By Weight
Compound III (free base)	15.01
Propylene Glycol (NF)	40.06
p-toluenesulfonic acid, monohydrate, Sigma	3.97
Tween® 80	5.05
Ethanol (USP, 200 proof)	2.52
Polyethylene glycol 540	33.4

This composition was prepared according to the process of Example 31.

Example 34 (capsule)

Component	% By Weight
Compound III (free base)	21.92
Propylene Glycol (NF)	25.64
Hydrochloric acid, reagent	5.85
Cremophor® RH40	3.76
Miglyol® 812	3.98
Ethanol (USP, 200 proof)	5.48
Gelucire® 44/14	33.4

This composition was prepared according to the process of Example 31 with the exception that the polyethylene glycol was replaced by Gelucire® 44/14 (which was warmed to no more than 10°C above its melting point).

Example 35 (capsule)

Component	% By Weight
Compound III (free base)	22.1
Propylene Glycol (NF)	25.75
Hydrochloric acid, reagent	5.90
Tween® 80	3.66
Miglyol® 812	3.73
Ethanol (USP, 200 proof)	5.56
Gelucire® 44/14	33.3

This composition was prepared according to the process of Example 31 with the exception that the polyethylene glycol was replaced by Gelucire® 44/14 (which was warmed to no more than 10°C above its melting point).

Example 36 (capsule)

Component	% By Weight
Compound III (free base)	21.78
Propylene Glycol (NF)	19.91
Hydrochloric acid, reagent	5.96
Cremophor® RH40	6.82
Miglyol® 812	6.73
Ethanol (USP, 200 proof)	5.51
Gelucire® 44/14	33.28

Ethanol (27.7 g) and compound III (110 g, screened through a 16 mesh screen) were mixed in a stainless steel container until the solution was clear to slightly cloudy. Propylene glycol (100.4 g) was added and mixing continued until the solution was clear to slightly cloudy. Miglyol® (33.8 g) was added and mixed well. Cremophor® (34.3 g) was added and mixed well. The hydrochloric acid was then added and mixed well. This solution was placed in a water jacketed vessel (Vessel A) at a temperature of about 10°C.

The Gelucire® (168.1 g) was placed in a water jacketed vessel (Vessel B) and heated to melt the Gelucire®. The water jacket was then maintained at a temperature of about 75°C.

An H&K 330 capsule filling machine with a liquid fill attachment was then used to fill the composition into hard gelatin capsules (No. 00, iron gray opaque).

Each vessel was connected via a separate circulation line through a separate metering pump into a nozzle head/block through which the appropriate volume of the contents of each of Vessels A and B was pumped, mixed and filled into the capsules. The rate of flow through each of the metering pumps was adjusted to provide the appropriate ratio of the contents of each of Vessels A and B to obtain the desired final composition in the filled capsules. If necessary, the circulation lines and nozzle head/block were equipped with a heating/cooling jacket or line to allow for temperature adjustment during capsule filling.

Example 37 (capsule)

Component	% By Weight
Compound III (free base)	18.03
Propylene Glycol (NF)	12.36
Hydrochloric acid, reagent	1.83
Citric acid (USP, anhydrous, powder)	4.12
Tween® 80	5.10
Cremophor® EL	17.51
Miglyol® 812	2.58
Ethanol (USP, 200 proof)	5.10
Gelucire® 44/14	33.38

This composition was prepared according to the process of Example 31 with the exception that the polyethylene glycol was replaced by Gelucire® 44/14 (which was warmed to no more than 10°C above its melting point).

Example 38 (capsule)

Component	% By Weight
Compound III (free base)	17.84
Propylene Glycol (NF)	12.36
Hydrochloric acid, reagent	1.87
Citric acid (USP, anhydrous, powder)	4.08
Tween® 80	5.20
Cremophor® EL	17.49
Miglyol® 812	2.69
Ethanol (USP, 200 proof)	5.13
Gelucire® 35/10	33.32

This composition was prepared according to the process of Example 31 with the exception that the polyethylene glycol was replaced by Gelucire® 35/10 (which was warmed to no more than 10°C above its melting point).

Example 39 (capsule)

Component	% By Weight
Compound III (free base)	21.68
Propylene Glycol (NF)	19.77
Hydrochloric acid, reagent	6.06
Cremophor® EL	6.87
Miglyol® 812	6.78
Ethanol (USP, 200 proof)	5.48
Gelucire® 35/10	33.36

This composition was prepared according to the process of Example 31 with the exception that the polyethylene glycol was replaced by Gelucire® 35/10 (which was warmed to no more than 10°C above its melting point).

Example 40 (capsule)

Component	% By Weight
Compound III (free base)	17.87
Propylene Glycol (NF)	12.12
Hydrochloric acid, reagent	1.92
Citric acid (USP, anhydrous, powder)	4.09
Cremophor® EL	17.61
Miglyol® 812	2.56
Tween® 80	5.38
Ethanol (USP, 200 proof)	5.18
Gelucire® 46/07	33.28

This composition was prepared according to the process of Example 31 with the exception that the polyethylene glycol was replaced by Gelucire® 46/07 (which was warmed to no more than 10°C above its melting point).

Example 41 (capsule)

Component	% By Weight
Compound III (free base)	18.05
Propylene Glycol (NF)	12.42
Hydrochloric acid, reagent	1.87
Citric acid (USP, anhydrous, powder)	4.11
Cremophor® EL	17.40
Miglyol® 812	2.61
Tween® 80	5.00
Ethanol (USP, 200 proof)	5.08
Gelucire® 50/13	33.46

This composition was prepared according to the process of Example 31 with the exception that the polyethylene glycol was replaced by Gelucire® 50/13 (which was warmed to no more than 10°C above its melting point).

Example 42 (capsule)

Component	% By Weight
Compound III (free base)	18.00
Propylene Glycol (NF)	12.31
Hydrochloric acid, reagent	1.90
Citric acid (USP, anhydrous, powder)	4.12
Cremophor® EL	17.65
Miglyol® 812	2.56
Tween® 80	5.10
Ethanol (USP, 200 proof)	5.17
Gelucire® 50/13	25.04
Neobee Oil M-5	8.35

This composition was prepared according to the process of Example 31 with the exception that the polyethylene glycol was replaced by Gelucire® 50/13 (which was warmed to no more than 10°C above its melting point) and that the Neobee Oil was added to the melted Gelucire® 50/13. This mixture was added to the solution resulting from Step 1.

Example 43 (capsule)

Component	% By Weight
Compound III (free base)	17.83
Propylene Glycol (NF)	12.20
Hydrochloric acid, reagent	1.88
Citric acid (USP, anhydrous, powder)	4.08
Cremophor® EL	17.48
Miglyol® 812	2.54
Tween® 80	5.02
Ethanol (USP, 200 proof)	5.12
Gelucire® 50/13	17.22
Gelucire® 35/10	16.64

This composition was prepared according to the process of Example 31 with the exception that the polyethylene glycol was replaced by a mixture of

Gelucire® 50/13 and Gelucire® 35/10 (which was warmed to no more than 10°C above its melting point).

Example 44 (capsule)

Component	% By Weight
Compound III (free base)	19.88
Citric acid (USP, anhydrous, powder)	2.01
Ethanol (USP, 200 proof)	8.12
Gelucire® 50/13	25.02
Neobee Oil M-5	24.86
N-methylpyrrolidinone	12.07
Vitamin E PEG 1000 succinate	8.04

Step 1. The compound of formula III was mixed with the N-methylpyrrolidone. To this mixture was added with mixing the ethanol and all of the remaining ingredients (except the Gelucire® 50/13 and the Neobee Oil).

Step 2. The Gelucire® 50/13 was warmed (to no more than 10°C above its melting point) until it was liquified. The liquified Gelucire® 50/13 was mixed with the Neobee Oil and this mixture was then added with mixing to the solution resulting from Step 1. The appropriate volume of this final mixture to provide the desired dose of compound III was filled into hard gelatin capsules.

Example 45 (capsule)

Component	% By Weight
Compound III (free base)	19.57
Citric acid (USP, anhydrous, powder)	1.99
Tween® 80	5.94
Ethanol (USP, 200 proof)	7.85
Gelucire® 44/14	32.28
N-methylpyrrolidinone	11.71
Vitamin E PEG 1000 succinate	4.92
Propyleneglycol monolaurate	14.73
Microcrystalline wax	1.00

Step 1. The compound of formula **III** was mixed with the N-methylpyrrolidinone. To this mixture was added with mixing the ethanol and all of the remaining ingredients (except the Gelucire® 44/14).

Step 2. The Gelucire® 44/14 was warmed (to no more than 10°C above its melting point) until it was liquified. The liquified Gelucire® 44/14 was then added with mixing to the solution resulting from Step 1. The appropriate volume of this final mixture to provide the desired dose of compound **III** was filled into hard gelatin capsules.

Example 46 (capsule)

Component	% By Weight
Compound **III** (free base)	18.20
Propylene Glycol (NF)	12.47
Hydrochloric acid, reagent	1.26
Cremophor® EL	11.23
Miglyol® 812	5.03
Tween® 80	5.13
Ethanol (USP, 200 proof)	14.11
Gelucire® 44/14	32.54

This composition was prepared according to the process of Example 31 with the exception that the polyethylene glycol was replaced by Gelucire® 44/14 (which was warmed to no more than 10°C above its melting point).

Example 47 (capsule)

Component	% By Weight
Compound **III** (free base)	18.22
Propylene Glycol (NF)	12.49
Hydrochloric acid, reagent	1.26
Cremophor® EL	11.24
Miglyol® 812	5.05
Tween® 80	5.14
Ethanol (USP, 200 proof)	14.12
Gelucire® 50/13	32.46

This composition was prepared according to the process of Example 31 with the exception that the polyethylene glycol was replaced by Gelucire® 50/13 (which was warmed to no more than 10°C above its melting point).

Example 48 (capsule)

Component	% By Weight
Compound III (free base)	17.72
Propylene Glycol (NF)	14.73
Hydrochloric acid, reagent	2.33
Cremophor® EL	11.81
Miglyol® 812	7.86
Ethanol (USP, 200 proof)	12.07
Gelucire® 44/14	33.48

This composition was prepared according to the process of Example 31 with the exception that the polyethylene glycol was replaced by Gelucire® 44/14 (which was warmed to no more than 10°C above its melting point).

Example 49 (capsule)

Component	% By Weight
Compound III (free base)	17.65
Propylene Glycol (NF)	14.67
Hydrochloric acid, reagent	2.32
Cremophor® EL	11.76
Miglyol® 812	7.83
Ethanol (USP, 200 proof)	12.02
Gelucire® 50/13	33.73

This composition was prepared according to the process of Example 31 with the exception that the polyethylene glycol was replaced by Gelucire® 50/13 (which was warmed to no more than 10°C above its melting point).

Example 50 (capsule)

Component	% By Weight
Compound III (free base)	19.62
Citric acid (USP, anhydrous, powder)	2.00
N-methylpyrrolidinone	10.94
Tween® 80	5.05
Vitamin E PEG 1000 succinate	4.95
propyleneglycol monolaurate	14.62
Ethanol (USP, 200 proof)	8.03
Gelucire® 44/14	33.76
Cab-o-sil®	1.03

The N-methylpyrrolidinone, Tween® 80, vitamin E PEG 1000 succinate and propyleneglycol monolaurate were mixed. The ethanol was added to the above mixture and stirred until the solution was clear to slightly cloudy. Then the citric acid was added and the mixture was stirred until it was clear to slightly cloudy. Compound III was added and the mixture was stirred until it was clear to slightly cloudy. The Gelucire® 44/14 was heated just enough to be liquified. The liquified Gelucire® 44/14 was added to the solution of the HIV protease inhibiting compound and stirred well. This solution was added slowly with mixing to the Cab-o-sil® and mixed well until the mixture was a dry solid. The resulting solid was passed through an appropriately sized seive to obtain granules. The appropriate amount of the granulation to provide the desired dose was filled into hard gelatin capsules.

Example 51 (capsule)

Component	% By Weight
Compound III (free base)	16.99
Propylene Glycol (NF)	13.50
Hydrochloric acid, reagent	1.91
Cremophor® EL	10.32
Miglyol® 812	4.99
Tween® 80	4.98
Ethanol (USP, 200 proof)	13.99
Gelucire® 50/13	33.30

This composition was prepared according to the process of Example 31 with the exception that the polyethylene glycol was replaced by Gelucire® 50/13 (which was warmed to no more than 10°C above its melting point).

Example 52 (capsule)

Component	% By Weight
Compound III (free base)	17.07
Propylene Glycol (NF)	14.00
Hydrochloric acid, reagent	1.90
Cremophor® EL	10.05
Miglyol® 812	4.83
Tween® 80	4.79
Ethanol (USP, 200 proof)	13.95
Gelucire® 50/13	33.38

This composition was prepared according to the process of Example 31 with the exception that the polyethylene glycol was replaced by Gelucire® 50/13 (which was warmed to no more than 10°C above its melting point).

Example 53 (capsule)

Component	% By Weight
Compound III (free base)	17.96
Propylene Glycol (NF)	14.96
Hydrochloric acid, reagent	1.99
Cremophor® EL	10.91
Tween® 80	5.90
Ethanol (USP, 200 proof)	14.98
Gelucire® 50/13	33.29

This composition was prepared according to the process of Example 31 with the exception that the polyethylene glycol was replaced by Gelucire® 50/13 (which was warmed to no more than 10°C above its melting point).

Example 54 (capsule)

Component	% By Weight
Compound III (free base)	13.00
Propylene Glycol (NF)	15.03
Hydrochloric acid, reagent	0.56
Cremophor® EL	13.05
Miglyol® 812	5.18
Tween® 80	5.00
Ethanol (USP, 200 proof)	14.89
Gelucire® 50/13	33.30

This composition was prepared according to the process of Example 31 with the exception that the polyethylene glycol was replaced by Gelucire® 50/13 (which was warmed to no more than 10°C above its melting point).

The remaining examples provide the preparation of compound III.

Example 55

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

A. N-(((Benzyl)oxy)carbonyl)-L-phenylalaninal.

A solution of 24.5 ml of anhydrous dimethyl sulfoxide in 870 ml of anhydrous dichloromethane was cooled under N_2 atmosphere to -60°C and treated over a period of 15 min with 131 ml of a 2 M solution of oxalyl chloride in dichloromethane in order that the internal temperature remained below -50°C. After addition, the solution was stirred at -60°C for 15 min and treated over a period of 20 min with a solution of 50 g (0.175 mol) of N-(((benzyl)oxy)-carbonyl)-L-phenylalaninol in 200 ml of dichloromethane. The resulting solution was stirred at -60°C for 1 h, then treated over a period of 15 min with 97 ml of triethylamine in order that the internal temperature remained below -50°C. After addition the solution was stirred at -60°C for 15 min, then, with the cooling bath in place, was treated rapidly (over a period of 1 min) with a solution of 163 g of citric acid in 550 ml of water. The resulting slurry was stirred vigorously for 10 min, allowed to warm, diluted to 1 liter with water, and separated. The organic layer was washed with 700 ml of water followed by a mixture of 550 ml of water and 150 ml of saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo at 20°C to give the crude desired compound as a light yellow solid.

B. (2S,3R,4R,5S)-2,5-Bis-(N-(((benzyl)oxy)carbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane and (2S,3S,4S,5S)-2,5-Bis-(N-(((benzyl)oxy)carbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

A suspension of 78.5 g of VCl_3·(tetrahydrofuran)$_3$ and 16 g of zinc dust in 400 ml of dry dichloromethane was stirred under N_2 atmosphere for 1 h at 25°C. A solution of 0.175 mol of N-(((benzyl)oxy)carbonyl)-L-phenylalaninal in 200 ml of dichloromethane was then added in one portion, and the resulting mixture was stirred at ambient temperature under N_2 atmosphere for 16 h. The resulting mixture was added to 500 ml of 1 M aqueous HCl, diluted with 500 ml of hot

chloroform, and shaked vigorously for 2 min. The layers were separated, and the organic layer was washed with 1 M aqueous HCl and separated. Filtration of the organic phase provided the crude desired product as a solid residue. The residue was slurried in 1.25 liters of acetone, treated with 5 ml of concentrated H_2SO_4, and stirred for 16 h at ambient temperature. The resulting mixture was filtered, and the residue (residue A) was washed with 50 ml of acetone. The combined filtrate was concentrated to a volume of 250 ml, diluted with 1000 ml of dichloromethane, washed three times with water and once with saturated brine, dried over $MgSO_4$, and concentrated to give a viscous oil. The oil was taken up in 1000 ml of 1 M HCl in methanol (prepared from 71 ml of acetyl chloride and 1000 ml of methanol) and stirred at ambient temperature for 2 h. The resulting precipitate was filtered, washed with methanol, and air-dried on the filter to provide 26.7 g of the desired compound as a white solid. The filtrate was concentrated and filtered to give a second crop (8.3 g) of (2S,3R,4R,5S)-2,5-bis-(N-(((benzyl)oxy)carbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane. ^1H NMR (d_6-DMSO) δ 2.59 (dd, J = 13, 5 Hz, 2 H), 2.74 (dd, J = 13, 9 Hz, 2 H), 3.26 (br, 2 H), 4.19 (m, 2 H), 4.54 (m, 2 H), 4.92 (m, 4 H), 6.82 (d, J = 9 Hz, 2 H), 7.0-7.35 (m, 20 H). Mass spectrum: $(M + H)^+ = 569$.

Residue A (above, 2.65 g) was suspended in 75 ml of tetrahydrofuran (THF) and 75 ml of 1 M aqueous HCl and heated at reflux for 24 h. After concentration of the resulting solution in vacuo, the residue was taken up in 10% methanol in chloroform, washed two times with water, dried over Na_2SO_4, and concentrated in vacuo to provide (2S,3S,4S,5S)-2,5-bis-(N-(((benzyl)oxy)carbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane as a white solid. ^1H NMR (d_6-DMSO) δ 2.64 (m, 2 H), 3.04 (m, 2 H), 3.49 (m, 2 H), 3.78 (m, 2 H), 4.70 (d, J = 7 Hz, 2 H), 4.93 (AA', 4 H), 7.1-7.4 (m, 20 H). Mass spectrum: $(M + H)^+ = 569$.

C. (2S,3R,4S,5S)-3-Acetoxy-2,5-bis-(N-(((benzyl)oxy)carbonyl)amino)-3-bromo-1,6-diphenylhexane.

A suspension of 25 g (44 mmol) of (2S,3R,4R,5S)-2,5-bis-(N-(((benzyl)oxy)carbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane in 500 ml of 2:1 dichloromethane/hexane was treated with 23 g of

α-acetoxyisobutyryl bromide. The resulting mixture was stirred at ambient temperature until the reaction clarified, washed with two 200 ml portions of saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo to give 30.8 g of the crude desired compound. A portion was purified by silica gel chromatography using 9:1 dichloromethane:ethyl acetate to provide the pure desired compound as a white solid. ^1H NMR ($CDCl_3$) δ 2.21 (s, 3 H), 2.62 (dd, J = 13, 11 Hz, 1 H), 2.75 (d, J = 7 Hz, 2 H), 2.95 (br d, J = 15 Hz, 1 H), 4.03 (br t, J = 10 Hz, 1 h), 4.40 (br d, J = 10 Hz, 1 H), 4.6-5.0 (m, 6 H), 5.12 (br d, J = 13 Hz, 1 H), 5.33 (br d, J = 11 Hz, 1 H), 7.0-7.4 (m, 10 H). Mass spectrum: $(M + NH_4)^+$ = 690, 692.

D. (2S,3R,4R,5S)-2,5-Bis-(N-(((benzyl)oxy)carbonyl)amino)-3,4-epoxy-1,6-diphenylhexane.

A solution of 35.56 g (52.8 mmol) of (2S,3R,4S,5S)-3-acetoxy-2,5-bis-(N-(((benzyl)oxy)carbonyl)amino)-3-bromo-1,6-diphenylhexane in 375 ml of dioxane was treated with 255 ml of 1N aqueous sodium hydroxide and stirred at ambient temperature for 16 h, during which the desired compound precipitated. The resulting mixture was filtered, and the residue was washed with water and dried to provide 22.23 g (76%) of the desired compound as a white solid. ^1H NMR ($CDCl_3$) δ 2.7-2.9 (m, 6 H), 3.9-4.0 (m, 2 H), 4.6-4.7 (m, 2 H), 5.03 (m, 4 H), 7.1-7.4 (m, 10 H).

E. (2S,3S,5S)-2,5-Bis-(N-(((benzyl)oxy)carbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

A mixture of 39.2 g (71.2 mmol) of (2S,3R,4R,5S)-2,5-bis-(N-(((benzyl)oxy)carbonyl)amino)-3,4-epoxy-1,6-diphenylhexane in 600 ml of THF was treated under N_2 atmosphere with 13 g (0.36 mol) of sodium borohydride. The resulting mixture was treated dropwise with 27.7 ml (0.36 mol) of trifluoroacetic acid. After being stirred for 3.5 h at ambient temperature, the resulting mixture was quenched with 1N aqueous HCl, diluted with water, and stirred for 16 h. The resulting mixture was filtered. washed with water, and dried to provide 22.85 g (58%) of the desired compound as a white solid.

F. (2S,3S,5S)-2,5-Diamino-1,6-diphenyl-3-hydroxyhexane.

A suspension of 32 g of the crude resultant compound of Example 55E and 55.5 g (176 mmol) of barium hydroxide octahydrate in 400 ml of 1,4-dioxane and 400 ml of water was heated at reflux for 4 h. The resulting mixture was filtered, and the residue was rinsed with dioxane. The combined filtrates were concentrated to a volume of approximately 200 ml and extracted with four 400 ml portions of chloroform. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography using first 2% isopropylamine in chloroform and then 2% isopropylamine/2% methanol in chloroform to provide 10.1 g (81%) of the pure desired compound as a white solid. ^1H NMR ($CDCl_3$) δ 1.54 (dt, J = 14, 10 Hz, 1 H), 1.67 (dt, J = 14, 3 Hz, 1 H), 2.50 (dd, J = 13, 8 Hz, 1 H), 2.58 (dd, J = 13, 8 Hz, 1 H), 2.8 (m, 2 H), 2.91 (dd, J = 13, 5 Hz, 1 H), 3.10 (m, 1 H), 3.72 (ddd, J = 11, 3, 2 Hz, 1 H), 7.1-7.4 (m, 10 H). Mass spectrum: $(M + H)^+ = 285$.

G. (4S,6S,1'S)-6-(1-Amino-2-phenylethyl)-4-benzyl-2-phenyl-3-aza-2-bora-1-oxacyclohexane.

A solution of 11.28 g (40 mmol) of (2S,3S,5S)-2,5-diamino-1,6-diphenyl-3-hydroxyhexane and 4.88 g (40 mmol) of phenylboric acid in 1 liter of toluene was heated at reflux and the water azeotropically removed with the aid of a Dean Stark trap until the distillate was clear. The solvent was then removed in vacuo to provide the crude desired compound which was used immediately without further purification.

H. Thioformamide.

To a cooled (0°C) 2 L three neck round bottom flask equipped with an overhead stirrer charged with a solution of formamide (30.5 mL, 0.76 mol) in 1 L of diethyl ether was added 89 g (0.19 mol) of phosphorous pentasulfide in small portions. The reaction mixture was allowed to warm to ambient temperature, stirred for 2 h, filtered, and concentrated in vacuo to afford thioformamide as a yellow offensive smelling oil which was used without purification.

I. Ethyl 2-Chloro-2-formylacetate.

To a three neck 2 L round bottom flask charged with potassium t-butoxide (0.5 mol, 500 mL of a 1 M solution in THF) and 500 mL of dry THF cooled to 0°C was added dropwise from an addition funnel a solution of ethyl chloroacetate (0.5 mol, 53.5 mL) and ethyl formate (0.5 mol, 40.4 mL), in 200 mL of THF over 3 hours. After completion of addition, the reaction mixture was stirred for 1 hour and allowed to stand overnight. The resulting solid was diluted with diethyl ether and cooled in an ice bath. Then, the pH was lowered to approximately 3 using 6N HCl. The organic phase was separated, and the aqueous layer was washed 3 times with diethyl ether. The combined ethereal portions were dried over $NaSO_4$, and concentrated in vacuo. The crude desired compound was stored at -30°C and used without further purification.

J. Ethyl Thiazole-5-carboxylate.

To a round bottom flask was added 250 mL of dry acetone, 7.5 g (0.123 mol) of thioformamide, and 18.54 g (0.123 mol) of ethyl 2-chloro-2-formylacetate. The reaction was heated at reflux for 2 hours. The solvent was removed in vacuo, and the residue was purified by chromatography (SiO_2, 6 cm o.d. column, 100% $CHCl_3$, R_f = 0.25) to provide 11.6 g (60%) of the desired compound as a light yellow oil. NMR ($CDCl_3$) δ 1.39 (t, J = 7 Hz, 3 H), 4.38 (q, J = 7 Hz, 2 H), 8.50 (s, 1 H), 8.95 (s, 1 H).

K. 5-(Hydroxymethyl)thiazole.

To a precooled (ice bath) three neck 500 mL flask containing lithium aluminum hydride (76 mmol) in 250 mL of THF was added ethyl thiazole-5-carboxylate (11.82 g, 75.68 mmol) in 100 mL of THF dropwise over 1.5 hours to avoid excess foaming. The reaction was stirred for an additional hour, and treated cautiously with 2.9 mL of water, 2.9 mL of 15% NaOH, and 8.7 mL of water. The solid salts were filtered, and the filtrate set aside. The crude salts were heated at reflux in 100 mL of ethyl acetate for 30 min. The resulting mixture was filtered, and the two filtrates were combined, dried over Na_2SO_4, and concentrated in vacuo. The product was purified by silica gel chromatography eluting sequentially with 0% - 2% - 4% methanol in chloroform, to provide the

desired compound, Rf = 0.3 (4% methanol in chloroform), which solidified upon standing in 75% yield. NMR ($CDCl_3$) δ 4.92 (s, 2 H), 7.78 (s, 1 H), 8.77 (s, 1 H). Mass spectrum: $(M + H)^+ = 116$.

L. ((5-Thiazolyl)methyl)-(4-nitrophenyl)carbonate.

A solution of 3.11 g (27 mmol) of 5-(hydroxymethyl)thiazole and excess N-methyl morpholine in 100 ml of methylene chloride was cooled to 0°C and treated with 8.2 g (41 mmol) of 4-nitrophenyl chloroformate. After being stirred for 1 h, the reaction mixture was diluted with $CHCl_3$, washed successively with 1N HCl, saturated aqueous $NaHCO_3$, and saturated brine, dried over $NaSO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography (SiO2, 1-2% MeOH/$CHCl_3$, Rf=0.5 in 4% MeOH/$CHCl_3$) to yield 5.9 g (78%) of the desired compound as a yellow solid. NMR ($CDCl_3$) δ 5.53 (s, 2 H), 7.39 (dt, J = 9, 3 Hz, 2 H), 8.01 (s, 1 H), 8.29 (dt, J = 9, 3 Hz, 2 H), 8.90 (s, 1 H). Mass spectrum: $(M + H)^+ = 281$.

M. (2S,3S,5S)-5-Amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane and (2S,3S,5S)-2-Amino-5-(N-((5-thiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

A solution of 500 mg (1.76 mmol) of (2S,3S,5S)-2,5-diamino-1,6-diphenyl-3-hydroxyhexane and 480 mg (1.71 mmol) of ((5-thiazolyl)methyl)-(4-nitrophenyl)carbonate in 20 ml of THF was stirred at ambient temperature for 4 h. After removal of the solvent in vacuo, the residue was purified by silica gel chromatography using first 2% then 5% methanol in chloroform to provide a mixture of the two desired compounds. Silica gel chromatography of the mixture using a gradient of 0 - 1 - 2% methanol in 93:2 isopropylamine: chloroform provided 110 mg (16%) of (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane (R_f 0.48, 96:2:2 chloroform:methanol:isopropylamine) and 185 mg (28%) of (2S,3S,5S)-2-amino-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane (R_f 0.44, 96:2:2 chloroform:methanol:isopropylamine).

(2S,3S,5S)-5-Amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane: NMR ($CDCl_3$) δ 1.3-1.6 (m, 2 H), 2.40 (dd, J = 14, 8 Hz, 1 H), 2.78 (dd, J = 5 Hz, 1 H), 2.88 (d, J = 7 Hz, 2 H), 3.01 (m, 1 H), 3.72 (br q, 1 H), 3.81 (br d, J = 10 Hz, 1 H), 5.28 (s, 2 H), 5.34 (br d, J = 9 Hz, 1 H), 7.07 (br d, J = 7 Hz, 2 H), 7.15 - 7.35 (m, 8 H), 7.87 (s, 1 H), 8.80 (s, 1 H). Mass spectrum: $(M + H)^+ = 426$.

(2S,3S,5S)-2-Amino-5-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane: NMR ($CDCl_3$) δ 1.55 (dt, J = 14, 8 Hz, 1 H), 1.74 (m, 1 H), 2.44 (dd, J = 15, 1 Hz, 1 H), 2.75 - 3.0 (m, 4 H), 3.44 (m, 1 H), 4.00 (br t, 1 H), 5.28 (m, 3 H), 7.1 - 7.4 (m, 10 H), 7.86 (s, 1 H), 8.80 (s, 1 H). Mass spectrum: $(M + H)^+ = 426$.

N. (2S,3S,5S)-5-Amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

A solution of 40 mmol of crude (4S,6S,1'S)-6-(1-amino-2-phenylethyl)-4-benzyl-2-phenyl-3-aza-2-bora-1-oxacyclohexane in 700 ml of anhydrous THF was cooled to -40°C and treated dropwise over a period of 1 h with a solution of 7.83 g (27.9 mmol) of ((5-thiazolyl)methyl)-(4-nitrophenyl)carbonate in 300 ml of dry THF. The resulting solution was allowed to warm to 0°C for 3 h, then to ambient temperature for 16 h. The solvent was removed in vacuo, and the residue was taken up in 700 ml of ethyl acetate, washed with three 150 ml portions of 1N aqueous NaOH and one 150 ml portion of brine. The organic phase was dried over Na_2SO_4 and concentrated in vacuo. Purification of the residue by silica gel chromatography using methanol/chloroform mixtures provided the desired compound mixed with its regioisomer. A second chromatography using 1-3% isopropylamine in chloroform provided 5.21 g of the desired compound which solidified upon standing.

O. 2-Methylpropane-thioamide.

A suspension of 100 g (1.15 mol) of isobutyramide in 4 L of diethyl ether was stirred vigorously and treated in portions with 51 g (0.115 mol) of P_4S_{10}.

The resulting mixture was stirred at ambient temperature for 2 h, filtered, and concentrated in vacuo to provide 94.2 g (80%) of the crude desired compound. ^{1}H NMR (DMSO-d_6) δ 1.08 (d, J = 7 Hz, 6 H), 2.78 (heptet, J = 7 Hz, 1 H), 9.06 (br, 1 H), 9.30 (br, 1 H). Mass spectrum: $(M + H)^+$ = 104.

P. 4-(Chloromethyl)-2-isopropylthiazole hydrochloride.

A mixture of 94.0 g (0.91 mol) of 2-methylpropane-thioamide, 115.7 g (0.91 mol) of 1,3-dichloroacetone, and 109.7 g (0.91 mol) of $MgSO_4$ in 1.6 liters of acetone was heated at reflux for 3.5 h. The resulting mixture was allowed to cool, filtered, and the solvent was removed in vacuo to provide the crude desired compound as a yellow oil. ^{1}H NMR (DMSO-d_6) δ 1.32 (d, J = 7 Hz, 6 H), 3.27 (heptet, J = 7 Hz, 1 H), 4.78 (s, 2 H), 7.61 (s, 1 H). Mass spectrum: $(M + H)^+$ = 176.

Q. 2-Isopropyl-4-(((N-methyl)amino)methyl)thiazole.

A solution of 40 g of 4-(chloromethyl)-2-isopropylthiazole hydrochloride in 100 ml of water was added dropwise with stirring to 400 ml of 40% aqueous methylamine. The resulting solution was stirred for 1 h, then concentrated in vacuo. The residue was taken up in chloroform, dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue by silica gel chromatography using 10% methanol in chloroform provided 21.35 g (55%) of the desired compound. ^{1}H NMR (DMSO-d_6) δ 1.34 (d, J = 7 Hz, 6 H), 2.56 (s, 3 H), 3.30 (heptet, J = 7 Hz, 1 H), 4.16 (s, 2 H), 7.63 (s, 1 H). Mass spectrum: $(M + H)^+$ = 171.

R. N-(((4-Nitrophenyl)oxy)carbonyl)-L-valine Methyl Ester.

A solution of 66.1 g (0.328 mol) of 4-nitrophenyl chloroformate in 1.2 liters of CH_2Cl_2 was cooled to 0°C and treated with L-valine methyl ester hydrochloride. The resulting mixture was treated slowly, with stirring, with 68.9 ml (0.626 mol) of 4-methylmorpholine. The resulting solution was allowed to slowly warm to ambient temperature and was stirred overnight. After washing with 3 portions of 10% aqueous $NaHCO_3$, the solution was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel

chromatography by eluting with chloroform to provide the desired compound. ^1H NMR (DMSO-d_6) δ 0.94 (d, J = 7 Hz, 3 H), 0.95 (d, J = 7 Hz, 3 H), 2.12 (octet, J = 7 Hz, 1 H), 3.69 (s, 3 H), 4.01 (dd, J = 8, 6 Hz, 1 H), 7.41 (dt, J = 9, 3 Hz, 2 H), 8.27 (dt, J = 9, 3 Hz, 2 H), 8.53 (d, J = 8 Hz, 1 H). Mass spectrum: $(M + NH_4)^+ = 314$.

S. N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine Methyl Ester.

A solution of 15.7 g (92 mmol) of 2-isopropyl-4-(((N-methyl)amino)-methyl)thiazole in 200 ml of THF was combined with a solution of 20.5 g (69 mmol) of N-(((4-nitrophenyl)oxy)carbonyl)-L-valine methyl ester. The resulting solution was treated with 1.6 g of 4-dimethylaminopyridine and 12.9 ml (92 mmol) of triethylamine, heated at reflux for 2 h, allowed to cool, and concentrated in vacuo. The residue was taken up in CH_2Cl_2, washed extensively with 5% aqueous K_2CO_3, dried over Na_2SO_4, and concentrated in vacuo. The resulting product mixture was purified by silica gel chromatography using chloroform as an eluent to provide 16.3 g (54%) of the desired compound. ^1H NMR (DMSO-d_6) δ 0.88 (d, J = 7 Hz, 3 H), 0.92 (d, J = 7 Hz, 3 H), 1.32 (d, J = 7 Hz, 3 H), 2.05 (octet, J = 7 Hz, 1 H), 2.86 (s, 3 H), 3.25 (heptet, J = 7 Hz, 1 H), 3.61 (s, 3 H), 3.96 (dd, J = 8, 7 Hz, 1 H), 4.44 (AA', 2 H), 6.58 (d, J = 8 Hz, 1 H), 7.24 (s, 1 H). Mass spectrum: $(M + H)^+ = 328$.

T. N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine.

A solution of 1.42 g (4.3 mmol) of the resultant compound of Example 55S in 17 ml of dioxane was treated with 17.3 ml of 0.50 M aqueous LiOH. The resulting solution was stirred at ambient temperature for 30 min, treated with 8.7 ml of 1 M HCl, and concentrated in vacuo. The residue was taken up in dichloromethane, washed with water, dried over Na_2SO_4, and concentrated in vacuo to provide 1.1 g (81%) of the desired compound. Mass spectrum: $(M + H)^+ = 314$.

U. (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane.

A solution of 70 mg (0.223 mmol) of N-((N-methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine, 79 mg (0.186 mmol) of (2S,3S,5S)-5-amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane, 30 mg (0.223 mmol) of 1-hydroxybenzotriazole hydrate, and 51 mg (0.266 mmol) of N-ethyl-N'-dimethylaminopropyl carbodiimide in 2 ml of THF was stirred at ambient temperature for 16 h. The resulting solution was concentrated in vacuo, and the residue was purified by silica gel chromatography using 97:3 CH_2Cl_2:CH_3OH to provide 100 mg (74%) of the desired compound (R_f 0.4, 95:5 CH_2Cl_2:CH_3OH) as a solid, mp 61-63°C. Mass spectrum: $(M + H)^+ = 721$. Anal. Calcd for $C_{37}H_{49}N_6O_5S_2 \cdot 0.5H_2O$: C, 60.88; H, 6.77; N, 11.51. Found: C, 60.68; H, 6.53; N, 11.36.

Example 56

(2S,3S,5S)-2-Amino-3-hydroxy-5-(t-butyloxycarbonylamino)-1,6-diphenylhexane.

Example 56A

(2S,3S,5S)-2-(N,N-dibenzylamino)-3-hydroxy-5-(t-butyloxycarbonylamino)-1,6-diphenylhexane.

To a stirred solution of (2S,3S,5S)-2-(N,N-dibenzylamino)-3-hydroxy-5-amino-1,6-diphenylhexane (10.0 g, 21.6 mmol) in tetrahydrofuran (200 mL) was added potassium carbonate (6.0 g, 43.2 mmol) in H_2O (200 mL). To this solution was added di-t-butyldicarbonate (5.64 g, 25.9 mmol) in tetrahydrofuran (10 mL). The solution which resulted was stirred at room temperature for 3 hours. N,N-dimethylethylenediamine (1 mL, 8.6 mmol) was added and the reaction mixture was stirred at room temperature for an additional hour. Ethyl acetate (400 mL) was added and the organic layer was separated and washed with 5% KH_2PO_4 (2 x 200 mL), water (1 x 200 mL), saturated $NaHCO_3$ (2 x 200 mL) and water (1 x 200 mL). The organic solution was then dried over sodium sulfate and

concentrated under reduced pressure to provide the desired product as a light yellow oil. 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.40 (s,9H), 1.58 (s, 2H), 2.45-2.85 (m, 4H), 3.05 (m, 1H), 3.38 (d, 2H), 3.6 (m, 1H), 3.79 (m, 1H), 3.87 (d, 2H), 4.35 (s, 1H), 4.85 (s, broad, 1H), 7.0-7.38 (m, 20 H).

Example 56B

(2S,3S,5S)-2-amino-3-hydroxy-5-(t-butyloxycarbonylamino)-1,6-diphenylhexane.

To a stirred solution of (2S,3S,5S)-2-(N,N-dibenzylamino)-3-hydroxy-5-(t-butyloxycarbonylamino)-1,6-diphenylhexane (12 g, 21.3 mmol) in methanol (350 mL) was charged ammonium formate (8.05 g, 128 mmol, 6.0 eq) and 10% palladium on carbon (2.4 g). The solution was stirred under nitrogen at 60 °C for three hours and then at 75 °C for 12 hours. An additional amount of ammonium formate (6 g) and 10% palladium on carbon (1.5 g) was added as well as 1 mL of glacial acetic acid. The reaction was driven to completion within 2 hours at a reflux temperature. The reaction mixture was then cooled to room temperature and then filtered through a bed of celite. The filter cake was washed with methanol (75 mL) and the combined filtrates were concentrated under reduced pressure. The residue was taken up in 1 N NaOH (300 mL) and extracted into methylene chloride (2 X 200 mL). The combined organic layers were washed with brine (250 mL) and dried over sodium sulfate. Concentration of the solution under reduced pressure provided the desired product as a light colored oil which slowly crystallized upon standing (5 g). Further purification of the product could be accomplished by flash chromatography (silica gel, 5% methanol in methylene chloride). 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9H), 1.58 (m, 1H), 1.70 (m, 1H), 2.20 (s, broad, 2H), 2.52 (m, 1H), 2.76-2.95 (m, 4H), 3.50 (m, 1H), 3.95 (m, 1H), 4.80 (d, broad, 1H), 7.15-7.30 (m, 10H).

Example 57

Alternative Preparation of (2S,3S,5S)-2-Amino-3-hydroxy-5-(t-butyloxycarbonylamino)-1,6-diphenylhexane.

Example 57A

(5S)-2-(*t*-Butyloxycarbonylamino)-5-(N,N-dibenzylamino)-1,6-diphenyl-4-oxo-2-hexene

To 9.21 gm (20 mmol) of (S)-2-amino-5-(N,N-dibenzylamino)-1,6-diphenyl-4-oxo-2-hexene and 0.37 gm (3 mmol) 4-*N,N*-dimethylaminopyridine in 100 ml of methyl *tert*-butylether was added *via* syringe pump a solution containing 4.80 gm (22 mmol) di-*tert*-butyl dicarbonate in the same solvent (25 ml) over a period of 6 h. An additional amount (3 ml) of methyl *tert*-butylether was then added to complete the addition. After stirring at room temperature for 18 h the reaction mixture was cooled with the aid of an ice water bath. The resultant solid was collected by suction filtration and washed with cold (0°C) methyl *tert*-butylether and hexane and dried under vacuum to give 9.9 gm of crude material as a white solid. The material thus isolated was disolved in a minimal amount of dichloromethane and purified by flash chromatography on silica gel. Elution of the column with a mixture of hexane-ethyl acetate-dichloromethane (8:1:1) gave, after concentration of the appropriate fractions, 8.1 gm (72%) of the desired compound. Mp. 191- 193°C. $[\alpha]_D$ -183.7° (c = 1.05, $CHCl_3$). ^1H NMR ($CDCl_3$, δ): 11.68 (bs, 1H), 7.05 - 7.47 (m, 20H), 5.28 (s,1H), 4.27 (d, J=16 Hz, 1H), 4.02 (d, J=16Hz, 1H), 3.58 (m, 4H), 3.40 (m, 1H), 3.11 (m, 1H), 2.90 (m, 1H), 1.48 (s, 9H).

Example 57B

Alternate preparation of (5S)-2-(*t*-Butyloxycarbonylamino)-5-(N,N-dibenzylamino)-1,6-diphenyl-4-oxo-2-hexene

A suspension of (S)-2-amino-5-(N,N-dibenzylamino)-1,6-diphenyl-4-oxo-2-hexene (100.0 g, 0.217 mol) in 15% ethyl acetate/hexanes (2 liters) under N_2 was warmed to about 40°C. The resulting solution was cooled to room temperature before adding 4.0 g (33 mmol) of N,N-dimethyl-4-aminopyridine and 49.7 g (0.228 mol) of di-tert-butyl dicarbonate. The reaction mixture was allowed to stir overnight at room temperature. (After approximately one hour, a white precipitate began to form.)

The suspension was filtered and the precipitate was washed with hexanes to afford the desired product as colorless crystals. TLC: 25% ethyl acetate/hexanes R_f 0.38.

Example 57C

(2S, 3S, 5S)-2-(N,N-Dibenzylamino)-5-(t-butyloxycarbonylamino)-3-hydroxy-1,6-diphenylhexane.

A solution of the product of Example 57A (5 g, 8.9mmol) in dichloromethane (100ml) and 1,4-dioxolane (100ml) was cooled to between -10° and -15° C and treated dropwise with 1M BH_3THF (26.7ml, 26.7mmol). The solution was stirred at this temperature for 3 hr. The clear solution was quenched with excess methanol (20ml) and stirred at room temperature for 30 min. The solvent was removed *in vacuo.*

The resulting white foam was dissolved in THF (75ml) and cooled to -40° C. A solution of LAH (9ml, 1M in THF, 9mmol) was added dropwise. After 10 min. the solution was quenched with water followed by dilute aqueous HCl. The organics were removed and the aqueous layer extracted with ethyl acetate (3 x 20 ml). The combined organics were washed (saturated aqueous bicarbonate followed by brine), dried (Na_2SO_4), filtered and evaporated to afford 4.9 g (99%) of the desired product as a white foam.

Alternatively, the white foam resulting from the BH_3THF reaction step was dissolved in MeOH (45ml), cooled to +3 °C and treated portionwise with KBH_4 (1.44 g, 26.7 mmol). After addition of the last portion of KBH_4 the reaction was stirred for an additional 4 hours at +4 to +5 °C. The solution was concentrated by 1/2 the volume *in vacuo*, diluted with 1/1 hexane-EtOAc (70 ml) and quenched (with cooling, maintain temp. <30 °C) by adding a 10 % solution of $KHSO_4$ to pH = about 5. NaOH (15 % aqueous) was added to pH = 12 - 13. The insoluble salts were removed by filtration, and the filter cake washed 3 times with 7 ml 1/1 hexane/EtOAc. The filtrate and washes were transferred to a separatory funnel, diluted with 15 ml hexane and 15 ml H_2O. The organics were removed and the aqueous layer was extracted once with 20 ml (1/1) hexane-EtOAc. The combined organics were washed (saturated brine), dried (Na_2SO_4), filtered, and evaporated to afford 5.2 g of the desired product which was used without further purification in subsequent reactions.

R_f 0.5 (25% EtOAc/hexane) ^1H NMR ($CDCl_3$) δ 7.37-7.10 (m 20H); 6.78 (br. s, 1H); 4.62 (d, 1H); 4.50 (s, 1H); 4.18 (dd, 1H); 3.9 (d, 2H); 3.65 (dd, 2H); 3.40 (d, 2H); 3.00 (m, 2H); 2.77 (m, 1H); 1.39 (s, 9H). MS (EI) *m/e*565 (M+H).

Example 57D

(2S, 3S, 5S)-2-Amino-3-hydroxy-5-(t-butyloxycarbonylamino)-1,6-diphenylhexane.

A solution of the product from Example 57C (150 gm, 250 mmol) dissolved in absolute EtOH (2 liters) was treated with 10 % Pd/C (18gm, pre-wetted), followed by addition of ammonium formate (78.6 gms, 1.25 moles) dissolved in H_2O (200ml). The resulting mixture was stirred at reflux for 2.5 hours. The mixture was cooled to room temperature and filtered through a pad of infusorial earth (20g). The filter cake was washed 3 times with EtOH (70ml each). The filtrate was concentrated *in vacuo*. The residue was dissolved into EtOAc (1 L) and washed (1 N NaOH, followed by H_2O, followed by brine), dried (Na_2SO_4), filtered and concentrated *in vacuo*. to a constant weight of 95 gms. (99.2 % of theory). The light yellow solid (91.5 gm of the 95 gm) was slurried in hot heptane (600 ml) (steam bath) and treated with isopropanol (45ml), and swirled to effect solution. The solution was allowed to slowly cool to room temperature over 3 hours, kept at room temperature for 2 more hours and filtered. The filter cake was washed 10 times with 9/1 hexane-isopropanol (30ml each) to give the desired product as an off-white finely crystalline solid which was dried to constant weight of 57.5 gm.

The crude product (20 gm) was recrystallized from hot 140 ml heptane/ 17 ml isopropanol. After letting the solution cool slowly to room temperature, the mixture was let stand at room temperature for 2 hours and then filtered. The filter cake was rinsed (5 X 15 ml (8/1) heptane/isopropanol) and dried to a constant weight of 18.5 gm.

Example 58

Alternative Preparation of (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

Example 58A

(2S,3S,5S)-5-(t-Butyloxycarbonylamino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

The product of Example 57D (6.0g , 15.6 mmoles) was dissolved in 60 mL of DMF under nitrogen atmosphere. To this stirred solution at room temperature was added 5-(p-nitrophenyloxycarbonyloxymethyl)thiazole (4.67g , 15.6 mmole) and the resulting solution was stirred for 4 h. The solvent was removed under reduced pressure by rotary evaporation and the residue dissolved in 150 mL EtOAc. This solution was washed with 5 x 75 mL 1 N NaOH solution, 100 mL brine, dried over Na_2SO_4. The solvent was removed to afford 8.02 g of a slightly yellowish oil. This material was crystallized from 30 mL EtOAc and 40 mL hexane to afford 6.53g (80%) of the desired product as a white solid. mp 118-120 °C H ^{1}NMR ($CDCl_3$) δ 8.79 (s, 1H), 7.83 (s, 1H), 7.30-7.15 (m, 8H), 7.08 (m, 2H), 5.23 (s, 2H), 5.14 (d, 1H, J = 9 Hz), 4.52 (m, 1H), 3.92-3.72 (m, 3H), 3.65 (m, 1H), 2.85 (d-apparent, 2H, J = 7.5 Hz), 2.72 (d-apparent, 2H, J = 7 Hz), 1.61 (m, 2H), 1.38 (s, 9H). CIMS m/z (526) $(M + H)^+$, 543 $(M + 18)^+$.

Example 58B

(2S,3S,5S)-5-Amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

The product of Example 58A (6.43g, 12.23 mmoles) was dissolved in 25 mL dioxane at room temperature under nitrogen atmosphere. To this stirred solution was added 20.25 mL of 4N HCl in dioxane, and after approximately 10 min a thick precipitate formed. An additional 10 mL of dioxane was added to loosen up the slurry. This mixture was stirred for 1 h and then filtered. The filter cake of the product bis-HCl salt was washed with 20 mL dioxane, air dried, and then dissolved in 175 mL water. To this solution was added 175 mL ethyl acetate and the two phase mixture rapidly stirred. The pH of this mixture was adjusted to pH = 10 by the dropwise addition of 3N NaOH to the rapidly stirred

mixture. The organic layer was isolated, washed with brine (150 mL), and dried over Na_2SO_4. The solvent was removed to afford 5.18g (99%) of the desired product as a clear oil. H^1 NMR ($CDCl_3$) δ 8.81 (s, 1H), 7.87 (s, 1H), 7.35-7.05 (m, 10 H), 5.33 (d, 1H, J = 9.3 Hz), 5.28 (m,2H), 3.81 (m, 1H), 3.72 (m, 1H), 3.01 (m, 1H), 2.88 (m, 2H), 2.78 (dd, 1H, J = 13.5, 5.1 Hz), 2.39 (dd, 1H, J = 9.0, 4.5 Hz), 1.57-1.30 (m, 2H). CIMS m/z 426 $(M + H)^+$.

Example 58C

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine (4.13g, 13.18 mmole) and hydroxybenztriazole (2.23g, 16.48 mmoles) were dissolved in 70 mL THF and then dicyclohexyl-carbodiimide(2.71g, 13.18 mmoles) was added in one portion to the stirred solution under nitrogen atmosphere. This mixture was stirred for 4h at room temperature and then filtered to remove dicyclohexylurea precipitate. (2S,3S,5S)-5-Amino-2-(N-((5-thiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane (5.1g, 11.99 mmoles) was dissolved in 100 mL THF under nitrogen atmosphere. To this stirred solution was added the filtrate of HOBT-active ester and the resulting solution was stirred at room temperature for 4 h, and the solvent removed via rotary evaporation. The residue was dissolved in 150 mL ethyl acetate and washed with 2 x 100 mL 1N NaOH, 100 mL brine, 100 mL of 1% w/w aqueous $KHSO_4$ and the solvent was removed by rotary evaporation to afford a residue. The residue was dissolved in 175 mL 1N HCL, and the solution filtered to remove the small quantity of dicyclohexylurea. The filtrate solution was added to 175 mL ethyl acetate and the two phase mixture rapidly mixed. The pH of this rapidly stirred mixture was adjusted to pH = 7 by dropwise addition of cold 3N NaOH. The organic layer was isolated, washed with 100 mL brine, dried over Na_2SO_4, filtered, and the solvent was removed to afford 8.6 g of a colorless foam. This material was crystallized from 42 mL EtOAc and 21 mL hexane to give 7.85g of the desired product as a white solid. mp = 122-123 °C. CIMS m/z 721 $(M + H)^+$.

Example 59

Alternative Preparation of (2S,3S,5S)-5-Amino-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

Alternative A

The product of Example 55F (9.5 g, 33.4 mmol) and phenylboronic acid (4.1 g, 33.6 mmol) were combined in toluene (150 mL) and refluxed for 2.5 hours with azeotropic water removal (Dean-Stark trap). Toluene (100 mL) was distilled out at atmospheric pressure, then the remaining toluene was removed under vacuum, to provide a yellow syrup which was dissolved in DMF (50 mL) and cooled to -60 °C. A solution of 5-(p-nitrophenyloxycarbonyloxy-methyl)thiazole (9.5 g, 33.5 mmol) in DMF (50 mL) was added over 45 minutes. The resulting mixture was stirred for 8 hours at -55±5 °C, then 14 hours at -25°C, then was allowed to warm to room temperature. The reaction mixture was diluted with 1 N HCl (250 mL) and washed with CH_2Cl_2 (2 x 80 mL). The combined organic layers were back-extracted with 1 N HCl (60 mL). The combined aqueous HCl layers were cooled in an ice-bath to 2 °C, and conc. (37%) HCL (30 mL) was added over 5 minutes. The desired product (bis HCl salt) began to precipitate within 30 minutes. The slurry was stirred 3 hours at 2-5 °C, then the product (bis HCl salt) was collected by filtration and dried in a vacuum oven at 55-60 °C. Yield 11.4 g (68%).

Second crop recovery:

The HCl mother liquors were stirred with ethyl acetate (190 mL) and neutralized to pH 9-10 with aqueous K_2CO_3 (200-300 g of 25% w/w K_2CO_3 was required). The ethyl acetate layer was concentrated under vacuum to an oil which was redissolved in 1 N HCl (90 mL) and washed with methylene chloride (45 mL). The aqueous layer was cooled to 2 °C. Conc. (37%) HCl (9.0 mL) was added to precipitate a second crop. After stirring for 1-3 hours at 2-5 °C, the solid was collected by filtration and dried in a vacuum oven at 55-60 °C. Yield 2.1 g (12.6%).

Neutralization of Bis HCl Salt:

The bis HCl salt (10.66 g, 21.4 mmol, mixture of first and second crops) was stirred with CH_2Cl_2 (110 mL) and 5% aqueous $NaHCO_3$ (110 mL) until all solids dissolved (2 hours). The aqueous layer was separated and extracted with another 50 mL CH_2Cl_2. The combined organic extracts were dried with Na_2SO_4 (10 g), filtered and concentrated under vacuum at ≤40 °C to an oil. The oil was dried on a vacuum pump to give the title compound as a yellow foam, 9.1 g (100 %).

Alternative B

The product of Example 51F (15.0 g, 0.053 mole) was dissolved in DMF (75 mL). Triisopropylborate (24.4 mL, 0.105 mole) was added and stirred at ambient temperature for approximately 1.5 hours. The solution was cooled to -10°C and a solution of 5-(p-nitorphenyloxycarbonyloxymethyl)thiazole (15.0 g, 0.054 mole) in DMF (75 mL) was added over 80 minutes. The reaction was stirred for approximately 1 hour at -10 °C, then was diluted with methylene chloride (250 mL) and quenched with a mixture of triethanolamine (24.8 g) and 5% aqueous sodium bicarbonate (300 mL). The biphasic mixture was stirred for 1 hour, then the layers were separated and the aqueous was extracted with another portion of methylene chloride (50 mL). The combined organic layers were extracted with 1N HCl (1 x 390 mL, then 1 x 95 mL). The acid layers were combined, cooled in an ice-bath, and further acidified with conc. HCl (50 mL) which produced a white slurry of product. The slurry was stirred for approximately 1 hour at 2°C. The desired product bis HCl salt) was collected by filtration and dried at 55 °C in a vacuum oven. Yield 18.5 g (70%).

Example 60

Alternative Preparation of (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane

To a solution of the product of Example 59 (9.1 g, 21.4 mmol), HOBT (3.6 g, 23.5 mmol) and N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)-carbonyl)-L-valine (7.37 g, 23.5 mmol) in THF (170 mL) was added DCC (4.85 g, 23.5 mmol). The solution was stirred at ambient temperature for 16 hours (DCU

precipitates). THF was removed under vacuum and the resulting paste was stirred with cold 1 N HCl (106 mL at 5 °C) for 3 hours to dissolve the the crude product. The DCU was removed by filtration and the filter cake was washed with 1 N HCl (30 mL). KH_2PO_4 (3.2 g) was dissolved in the combined HCl filtrates. The solution was mixed with ethyl acetate (80 mL) and neutralized to pH 7 with aqueous NaOH (60.3 g of 10% w/w NaOH). The aqueous layer was extracted with another 25 mL ethyl acetate and the combined ethyl acetate extracts were washed with aqueous $NaHCO_3$ (2 x 37 mL of 5% w/w $NaHCO_3$). The organic layer was dried with Na_2SO_4 (13 g), filtered, and concentrated under vacuum at ≤45 °C. The residue was dissolved in a 1:1 ethyl acetate/heptane mixture (200 mL) at 70 °C. The solution was allowed to cool slowly and stirred overnight at room temperature to provide a thick slurry. The product was collected by filtration and washed with 1:1 ethyl acetate/heptane (20 mL). The product was dried briefly at 55 °C in a vacuum oven to obtain an approximate weight prior to the second crystallization (12.85 g, 83%).

A second crystallization from 144 mL of 2:1 ethyl acetate/heptane (dissolved at ~70 °C, then stirred at room temperature 12 hours) produced a thick slurry of fine white solid. The product was collected by filtration and washed with 15 mL 2:1 ethyl acetate/heptane, then dried in a vacuum oven at 55 °C for 2 days to give the desired product. Yield 11.9 g (77%).

Example 61
Alternate Preparation of ((5-Thiazolyl)methyl)-(4-nitrophenyl)carbonate

Example 61A
2-Amino-5-(ethoxycarbonyl)thiazole Hydrochloride

To a -10 °C solution of potassium tert-butoxide (110 g, 0.98 mol) in THF (1.9 L) was added a solution of ethyl chloroacetate (100 mL, 0.934 mol) and ethyl formate (75 mL, 0.928 mol) in THF (400 mL) dropwise over 2 hours, with good mechanical stirring. The thick solution was stirred another 2 hours at ca. -1 °C then the reaction was quenched by addition of a solution of NaCl (150 g) in 1 N HCL (750 mL). The mixture was allowed to warm to 20 °C and the lower aqueous layer (containing some precipitated salt) was separated. The organic

layer was stripped under vacuum on a rotary evaporator. The oil was redissolved in 500 mL ethyl acetate, dried with 75 g Na_2SO_4 for 1 hour, filtered and concentrated under vacuum (40-50 °C bath temperature) to an oil. The resulting crude chloroaldehyde (161 g) and thiourea (70 g, 0.92 mol) were dissolved in THF (2 L) and warmed to gentle reflux (60 °C). The thiourea dissolved during warming, and within 20 minutes, product precipitated from solution. After 100 minutes the suspension was allowed to cool to room temperature, then was cooled in an ice-bath for 1 hour. The product was collected on a fritted Buchner funnel and washed with 2 x 100 mL cold THF, then dried overnight in a vacuum oven at 50 °C. Yield: 122 g of title compound as a tan-colored solid, m.p. 182-185 °C (dec.). ^{1}H NMR (DMSO-d_6) δ 7.86 (s, 1H), 4.19 (q, 2H), 1.21 (t, 3H). ^{13}C NMR (DMSO-d_6) δ 171.9, 160.4, 140.4, 114.4, 61.1, 14.2.

Example 61B

2-Amino-5-(ethoxycarbonyl)thiazole

To a -10 °C solution of potassium tert-butoxide (150 g, 1.3 mol) in THF (1.35 L) was added a solution of ethyl chloroacetate (139 mL, 1.3 mol) and ethyl formate (103 mL, 1.27 mol) in THF (150 mL) dropwise over 75 minutes, with good mechanical stirring. A THF rinse (25 mL) was added over 5 minutes. The thick solution was stirred another 3 hours at ca. -5 to 0 °C, then the reaction was quenched by addition of a solution of NaCl (240 g) and conc. HCl (90 mL) in water (960 mL). The mixture was allowed to warm to 15 °C and the lower aqueous layer was discarded. Thiourea (97 g, 1.27 mol) was dissolved in the crude THF solution of chloroaldehyde. The solution was warmed to 65 °C and refluxed for 1 hour, then cooled to 30 °C. Addition of a solution of K_2CO_3 (88g, 0.64 mol) in 1500 mL water produced two layers (aqueous pH=7). The THF was removed under vacuum at ≤45 °C, causing the product to precipitate as a yellow solid. The slurry was cooled to 15 °C, and the product was collected on a fritted Buchner funnel and washed with 3 x 200 mL water, then dried 24 hours in a vacuum oven at 55 °C to provide 151 g of title compound as a yellow solid, m.p. 155-158 °C. ^{1}H NMR (DMSO-d_6) δ 7.8 (br s, 2H, NH_2), 7.62 (s, 1H), 4.13 (q, 2H), 1.18 (t, 3H). ^{13}C NMR (DMSO-d_6) δ 173.4, 161.3, 147.9, 114.5, 60.1, 14.3.

Example 61C

5-(Ethoxycarbonyl)thiazole

A solution of 2-amino-5-(ethoxycarbonyl)thiazole (50 g, 0.29 mmol) in a mixture of DMF (83 mL) and THF (317 mL) was added dropwise over 87 minutes to a stirred 41 °C solution of isoamyl nitrite (59 mL, 0.44 mol) in DMF (130 mL). A maximum temperature of 60 °C was observed during the exothermic addition. After another 40 minutes the THF was removed under vacuum at 45 °C. The concentrated DMF solution was cooled to 25 °C and diluted with toluene (420 mL) and water (440 mL). The toluene layer was extracted with 3 x 120 mL water, then dried with Na_2SO_4 (50 g) for 1 hour. After filtration the toluene layer was stripped on a rotary evaporater at 50 °C bath temperature, then on a vacuum pump at 21 °C. The crude residue containing the title compound weighed 65.6 g. This material was used directly in the next step. A sample of similarly prepared material was purified by column chromatography to give a yellow oil. ^1H NMR ($CDCl_3$) δ 8.95 (s, 1H), 8.51 (s, 1H), 4.39 (q, 2H), 1.40 (t, 3H). ^{13}C NMR ($CDCl_3$) δ 161.0, 157.9, 148.6, 129.8, 61.6, 14.1.

Example 61D

5-(Hydroxymethyl)thiazole

To a slurry of lithium aluminum hydride (9.0 g) in THF (633 mL) was added a solution of crude 5-(ethoxycarbonyl)thiazole (65.6 g from Example 61C) in THF (540 mL) over 95 minutes at 0-5 °C. After an additional 25 minutes, the reaction was quenched at 5 °C by sequential addition of water (8.1 mL), 15% NaOH (8.1 mL), and water (24.3 mL). After drying with Na_2SO_4 (44 g) for 2 hours, the slurry was filtered, and the filter cake was washed with 100 mL THF. The combined filtrates were concentrated under vacuum at 45 °C to a brown oil (39 g). The oil was fractionally distilled through a short-path apparatus. The product fractions distilled at 97-104 °C vapor temperature at 3-5 mm, providing 20.5 g of the title compound as a turbid orange oil. ^1H NMR ($CDCl_3$) δ 8.74 (s, 1H), 7.72 (s, 1H), 4.89 (s, 2H), 3.4 (br s, 1H, OH). ^{13}C NMR ($CDCl_3$) δ 153.4, 140.0, 139.5, 56.6.

Example 61E

5-(p-Nitrophenyoxycarbonyloxymethyl)thiazole Hydrochloride

Distilled 5-(hydroxymethyl)thiazole (14.1 g, 123 mmol) and triethylamine (17.9 mL, 129 mmol) were dissolved in ethyl acetate (141 mL) and cooled to -1 °C (ice/salt bath). A solution of 4-nitrophenyl chloroformate (26.0 g, 129 mmol) dissolved in ethyl acetate (106 mL) was added dropwise over 50 minutes at an internal temperature of 0-4 °C. An ethyl acetate flask rinse (20 mL) was also added. Salts precipitated from solution throughout the addition. The yellow mixture was stirred another 1 hour 45 minutes at 0-2 °C, then a solution of dilute HCl (3.1 g, 31 mmol of conc. HCl in 103 mL water) was added at once. The mixture was stirred for 0.5 hours while warming to 15 °C, then stirring was stopped. The organic layer was washed twice with aqueous 5% K_2CO_3 solution (2 x 70 mL), then dried with Na_2SO_4 (30 g). After filtration the solution was concentrated under vacuum on a rotary evaporater (bath temperature of 41 °C) to a brown oil (38g). The crude 5-(p-nitrophenyoxycarbonyloxymethyl)-thiazole was dissolved in ethyl acetate (282 mL), then cooled in an ice bath to 2 °C. Dry HCl gas (7.1 g, 195 mmol) was bubbled in slowly over 50 minutes (temperature 2-4 °C). After stirring for another 1 hour 45 minutes at 2-4°C, the solid precipitate was collected on a sintered glass funnel under a nitrogen blanket and the flask was washed out with 50 mL cold ethyl acetate which was used to rinse the filter cake. The cake was dried on the funnel under strong nitrogen purge for 15 minutes then dried in a vacuum oven at 50 °C with a nitrogen purge to provide 29.05 g of the title compound as tan powder, m.p. 131-135 °C (dec.). ^1H NMR (DMSO-d_6) δ 9.21 (d, 1H), 8.27 (m, 2H), 8.06 (d, 1H), 7.52 (m, 2H), 5.54 (s, 2H). ^{13}C NMR (DMSO-d_6) δ 157.3, 155.2, 151.8, 145.3, 143.7, 131.9, 125.5, 122.7, 62.1.

Example 61F

5-(p-Nitrophenoxycarbonyloxymethyl)thiazole

5-(p-Nitrophenoxycarbonyloxymethyl)thiazole hydrochloride (3.0 g) was slurried in ethyl acetate (30 mL) and cooled to 10-15 °C. A solution of 5% aqueous potassium carbonate (30 mL) was added with rapid stirring. After 15 minutes, stirring was stopped and the aqueous layer was separated.

layer was dried with Na_2SO_4 (3 g), filtered, and solvent was under vacuum to give 2.49 g of the title compound as a brown syrup solidified, m.p. 62-64 °C. ^1H NMR ($CDCl_3$) δ 8.90 (d, 1H), 8.29 (m, 1H), 7.39 (m, 2H), 5.52 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 155.4, 155.2, 145.4, 144.9, 130.6, 125.3, 121.6, 61.9.

Example 62
Alternative Preparation of N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine

Example 62A
Thioisobutyramide

To a 1 liter three neck round bottom flask equipped with mechanical , nitrogen atmosphere, condensor, thermocouple and 15 ° C water bath harged (26.0 g, 0.298 mols) isobutyramide followed by (19.9 g, 0.045 phosphorous pentasulfide and 375 mls THF. This solution was stirred at 5 ° C for 3 hours, then was warmed to 60 °C and stirred an additional 3 . The THF was removed under vacuum with a 50 ° C bath temperature to a yellow oil. This oil was neutralized with a solution of 5 g NaOH, 10 g and 90 g water. Next the product was extracted into EtOAc (2 X 250 mls) the combined organics reduced under vacuum to an oil. The oil was olved in 50 mls THF and again the solvent was removed under vacuum to the desired product as a yellow oil. (yield approx. 27 grams, 88%).

Example 62B
2-Isopropyl-4-(((N-methyl)amino)met[illegible])thiazole

The thioisobutyramide resulting from Example 62A was dissolved in 70 THF and added slowly to a solution of (34.1 g , .27 mols) 1,3-dichloracetone 40 mls THF. A 10 ml rinse of THF was used to completely transfer the amide. The reaction wass carried out in a 250 ml flask with mechanical under nitrogen atmosphere. The reaction temperature was maintained low 25 ° C during addition with a 15 ± 5 ° C bath. The bath was kept in place

for 1 hour after which it was removed and the reaction stirred for 18 hours. Next this stirred chloromethyl-thiazole solution was added to 376 mls (4.37 mols) 40 % aqueous methylamine solution at 15 ° C in a 1 liter flask. The temperature was maintained below 25 ° C during addition. After half an hour the bath was removed and the reaction stirred for 3 hours at ambient temperature. The solvent was removed under vacuum with a 50 ° C bath to an end volume of 310 mls. The residue was then basified with 50 g 10 % NaOH to pH 12 and extracted into methylene chloride (2 X 160 mls). The combined organics were then washed with 1 X 150 g of 20 % ammonium chloride followed by 1 X 90 g of 20 % ammonium chloride. The combined aqueous washes were then back extracted with 150 mls methylene chloride. The combined product methylene chloride layers were then extracted with 100 g of a solution of 25 g conc. HCl and 75 g water. This acidic product solution was then washed with 135 mls methylene chloride. Next the acidic product solution was cooled, then neutralized with 100 g 20 % NaOH solution. The product was extracted from this mixture with methylene chloride (2 X 135 mls). The solvent was removed under vacuum to afford the desired product as an amber oil. (yield approx. 28 grams)

Example 62C

N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine Methyl Ester

Into a 500 ml 3-neck round bottom flask equipped with mechanical stirrer, nitrogen atmosphere, thermocouple, heating mantle and condensor was charged the product of Example 62B (28.1 g, .165 mols), phenoxycarbonyl-(L)-valine (41.5 g, .165 mol) and 155 ml toluene. This solution was warmed to reflux (110 °C) and stirred for three hours, then cooled to 20± 5° C and washed with 2 X 69 ml 10 % citric acid followed by 1X 69 ml water, 1 X 116 mls 4 % sodium hydroxide, 1X 58 ml 4 % sodium hydroxide and finally 1X 58 ml water. The organic product solution was then treated with 3 grams of activated carbon at reflux for 15 minutes , filtered through infusorial earth to remove carbon, and the carbon/infusorial earth cake was washed with 25 ml hot toluene. Next the solvent was removed to afford a brown oil which solidifed upon cooling. This brown solid was dissolved with warming in 31 ml EtOAc and 257 ml heptane at 50±5° C. This solution was slowly cooled to 25 °C, stirred 12 hours, cooled

further to 0°C, and stirred 3 hours. The crystals were collected by filtration and washed with 50 ml 1:9 EtOAc/Heptane. The solid was dried in a 50°C vacuum oven for 12 hours to afford 41.5 grams of the desired product as a tan-colored solid (76.9%).

Example 62D

N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine

To a one liter three neck flask was charged the product of Example 62C (50 g, 0.153 mol), lithium hydroxide monohydrate (13 g, 0.310 mol), 200 ml THF and 190 ml water. This hazy solution was stirred for 2 hours. The reaction was quenched with a solution of conc. HCl (32.4 g, 0.329 mol) in 65 mL water, the THF was removed under vacuum and the product extracted into methylene chloride (3 X 210 ml). (NOTE: If necessary, the pH of the aqueous layer should be adjusted to maintain pH 1-4 during the extractions.) The combined organics were then dried with 50 g sodium sulfate, filtered with a 150 ml methylene chloride rinse of the sodium sulfate, and the solvent was removed under vacuum. The product was dissolved in 450 ml THF and again the solvent was removed. Next the product was dissolved in 475 ml THF containing 0.12 g butylated hydroxytoluene (BHT) for storage. If desired, the solvent can be removed under vacuum and the residual syrup dried in a vacuum oven at 55 °C to provide a glassy solid.

The above process for the preparation of compound III is disclosed in PCT Patent Application No. WO94/14436, published July 7, 1994, which is hereby incorporated herein by reference.

Protocol For Oral Bioavailability Studies

Dogs (beagle dogs, mixed sexes, weighing 7-14 kg) were fasted overnight prior to dosing, but were permitted water ad libitum. Each dog received a 0.5 mg/kg subcutaneous dose of histamine approximately 30 minutes prior to dosing. Each dog received a single solid dosage form corresponding to a 5 mg/kg dose of the drug. The dose was followed by approximately 10 milliliters of water. Blood samples were obtained from each animal prior to dosing and 0.25, 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 10 and 12 hours after drug administration. The plasma

was separated from the red cells by centrifugation and frozen (-30°C) until analysis. Concentrations of parent drug were determined by reverse phase HPLC with low wavelength UV detection following liquid-liquid extraction of the plasma samples. The parent drug area under the curve was calculated by the trapezoidal method over the time course of the study. The absolute bioavailability of each test composition was calculated by comparing the area under the curve after oral dosing to that obtained from a single intravenous dose. Each capsule or capsule composition was evaluated in a group containing at least six dogs; the values reported are averages for each group of dogs. The average bioavailability data for the compositions of the Examples is shown in Table I.

TABLE 1

Example No.	Mean % Bioavailability
Example 1	0.0
Example 2	0.0
Example 3	2.5
Example 4	37.4
Example 5	36.2
Example 6	55.7
Example 7	42.1
Example 8	87.8
Example 9	58.4
Example 10	25.8
Example 11	64.1
Example 12	100
Example 13	39.6
Example 14	93.9
Example 15	73.4
Example 16	76.8
Example 17	94.1
Example 18	73.3
Example 20	56.0
Example 21	100
Example 22	53.3
Example 23	52.4
Example 24	58.5
Example 25	69.9
Example 26	54.0

Example No.	Mean % Bioavailability
Example 27	100
Example 28	93.3
Example 29	55.5
Example 31	53.3
Example 32	52.4
Example 33	58.5
Example 34	69.9
Example 35	54.0
Example 36	100
Example 37	93.3
Example 38	89.6
Example 39	100
Example 40	61.5
Example 41	76.2
Example 42	82.4
Example 43	75.7
Example 44	49.9
Example 45	84.1
Example 46	79.2
Example 47	100
Example 51	100
Example 52	93.2
Example 53	61.5
Example 54	76.4

This data indicates that solution compositions provided significantly better bioavailability than non-formulated compound **III**. Additionally, the solution composition, encapsulated in hard gelatin capsule or soft elastic capsule, demonstrated greatly improved bioavailability. Additionally, the solid composition, encapusaled in a gelatin capsule, demonstrated greatly improved bioavailability.

Compounds **I**, **II** and **III** are inhibitors of HIV-1 and HIV-2 protease. They are useful for inhibiting an HIV infection and treating AIDS in humans. Total daily dose of compound **I**, **II** or **III** administered to a human in single or divided doses may be in amounts, for example, from 0.001 to 1000 mg/kg body weight daily but more usually 0.1 to 50 mg/kg body weight daily. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose. It will

be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, rate of excretion, drugs administered in combination and the severity of the particular disease undergoing therapy.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds, methods and compositions. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.

The claims defining the invention are as follows:

1. A pharmaceutical composition comprising a solution of (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)-valinyl)amino)-2-(N-((5-thiazolyl)methoxy-carbonyl)amino)-1,6-diphenyl-3-hydroxyhexane in a pharmaceutically acceptable organic solvent, the solvent comprising a pharmaceutically acceptable alcohol.

2. The composition of claim 1 wherein the solution is encapsulated in a hard gelatin capsule or a soft elastic gelatin capsule.

3. The composition of claim 1 or claim 2 further comprising a pharmaceutically acceptable acid.

4. The composition of any one of claims 1-3 further comprising an additive or a mixture of additives independently selected from glycerin, pharmaceutically acceptable surfactants and antioxidants.

5. A pharmaceutical composition comprising a solution of

(a) (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane; and

(b) a pharmaceutically acceptable acid or a combination of pharmaceutically acceptable acids in a pharmaceutically acceptable organic solvent, the solvent comprising a pharmaceutically acceptable alcohol.

6. The composition of claim 5 wherein the solution is encapsulated in a hard gelatin capsule or a soft elastic gelatin capsule.

7. The composition of claim 5 or claim 6 further comprising water.

8. The composition of any one of claims 5-7 further comprising an additive or a mixture of additives independently selected from glycerin, pharmaceutically acceptable surfactants and antioxidants.

9. The composition of claim 5 comprising a solution of

(a) from about 2% to about 30% by weight of the total solution of (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)-valinyl)amino)-2-(N-((5-thiazolyl)-methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane; and

(b) from about 0.2 molar equivalent to about 3 molar equivalents, based upon the amount of the compound of part (a), of a pharmaceutically acceptable acid or a mixture of pharmaceutically acceptable acids in a pharmaceutically acceptable organic solvent, the solvent comprising a pharmaceutically acceptable alcohol and the solvent comprising from about 50% to about 95% by weight of the total solution.

10. The composition of claim 9 wherein the solution is encapsulated in a hard gelatin capsule or a soft elastic gelatin capsule.

11. The composition of claim 9 comprising a solution of (1) (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)-valinyl)amino)-2-(N-((5-thiazolyl)methoxy-carbonyl)amino)-1,6-diphenyl-3-hydroxyhexane in the amount of from about 2% to about 30% by weight of the total solution and (2) a total of from about 0.2 to about 2 molar equivalents (based on the compound of part (1)) of (i) a pharmaceutically acceptable acid or (ii) a mixture of

AUSTRALIAN PATENT OFFICE

pharmaceutically acceptable acids in a pharmaceutically acceptable organic solvent comprising a mixture of (a) a pharmaceutically acceptable alcohol or mixture of pharmaceutically acceptable alcohols in a total amount of from about 2% to about 50% by weight of the total solution, said alcohol or mixture of alcohols being a liquid at room temperature and (b) a pharmaceutically acceptable organic solvent or a mixture of pharmaceutically acceptable organic solvents in a total amount of from about 20% to about 60% by weight of the total solution, said solvent or mixture of solvents having a melting point between about 20°C and about 60°C, said solvent or mixture of solvents being miscible with the alcohol or mixture of alcohols and providing a homogenous mixture with the alcohol or mixture of alcohols, said homogenous mixture being a solid or semi-solid at about 20°C, wherein the solution is encapsulated in a soft elastic capsule or a hard gelatin capsule.

12. The composition of claim 11 comprising a solution of (1) (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)-valinyl)amino)-2-(N-((5-thiazolyl)methoxy-carbonyl)amino)-1,6-diphenyl-3-hydroxyhexane in the amount of from about 2% to about 30% by weight of the total solution and (2) a total of from about 0.2 to about 2 molar equivalents (based on the compound of part (1)) of (i) a pharmaceutically acceptable acid or (ii) a mixture of pharmaceutically acceptable acids in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of from about 5% to about 40% by weight of the total solution, (b) ethanol in the amount of from about 2% to about 20% by weight of the total solution, and (c) polyethylene glycol 540 in the amount of from about 20% to about 60% by weight of the total solution or a total amount of from about 20% to about 60% by weight of the total solution of (i) a saturated polyglycolized glyceride or (ii) a mixture of saturated polyglycolized glycerides, wherein the solution is encapsulated in a soft elastic capsule or a hard gelatin capsule.

13. The composition of claim 12 comprising a solution of (1) (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)-valinyl)amino)-2-(N-((5-thiazolyl)methoxy-carbonyl)amino)-1,6-diphenyl-3-hydroxyhexane in the amount of from about 20% to about 25% by weight of the total solution and (2) a total of from about 1.5 to about 2 molar equivalents (based on the compound of part (1)) of hydrochloric acid in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of from about 20% to about 22% by weight of the total solution, (b) ethanol in the amount of from about 5% to about 6% by weight of the total solution, and (c) a saturated polyglycolized glyceride in the amount of from about 30% to about 35% by weight of the total solution, wherein the solution is encapsulated in a hard gelatin capsule.

14. The composition of claim 12 comprising a solution of (1) (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)-valinyl)amino)-2-(N-((5-thiazolyl)methoxy-carbonyl)amino)-1,6-diphenyl-3-hydroxyhexane in the amount of from about 15% to about 20% by weight of the total solution and (2) a total of from about 0.3 to about 0.6 molar equivalents (based on the compound of part (1)) of hydrochloric acid in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of about 12% by weight of the total solution, (b) ethanol in the amount of from about 5% to about 6% by weight of the total solution, and (c) a saturated polyglycolized glyceride in the amount of from about 30% to about 35% by weight of the total solution, wherein the solution is encapsulated in a hard gelatin capsule.

OFFICE

15. The composition of claim 12 comprising a solution of: (1) (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)-valinyl)amino)-2-(N-((5-thiazolyl)methoxy-carbonyl)amino)-1,6-diphenyl-3-hydroxyhexane in the amount of from about 15% to about 20% by weight of the total solution in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of about 40% by weight of the total solution, (b) ethanol in the amount of about 2% to about 3% by weight of the total solution, and (c) polyethylene glycol 540 in the amount of from about 30% to about 35% by weight of the total solution, wherein the solution is encapsulated in a hard gelatin capsule.

16. The composition of claim 12 comprising a solution of (1) (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)-valinyl)amino)-2-(N-((5-thiazolyl)methoxy-carbonyl)amino)-1,6-diphenyl-3-hydroxyhexane in the amount of from about 15% to about 20% by weight of the total solution and (2) a total of from about 0.3 to about 0.6 molar equivalents (based on the compound of part (1)) of hydrochloric acid in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of about 12% by weight of the total solution, (b) ethanol in the amount of from about 10% to about 15% by weight of the total solution, and (c) a saturated polyglycolized glyceride in the amount of from about 30% to about 35% by weight of the total solution, wherein the solution is encapsulated in a hard gelatin capsule.

17. The composition of claim 9 comprising a solution of (a) about 8.8% by weight of the total solution of (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane; and (b) about 2 molar equivalents, based upon the amount of the compound of part (a), of hydrochloric acid in a mixture comprising about 82% by weight of the total solution of propylene glycol, about 3.5% by weight of the total weight of the solution of ethanol and about 4.4% by weight of the total solution of water.

18. The composition of claim 17 wherein the solution is encapsulated in a hard gelatin capsule.

19. The composition of claim 12 comprising a solution of (1) (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)-valinyl)amino)-2-(N-((5-thiazolyl)methoxy-carbonyl)amino)-1,6-diphenyl-3-hydroxyhexane in the amount of from about 4% to about 30% by weight of the total solution and (2) a total of about two molar equivalents (based on the compound (1)) of (i) a pharmaceutically acceptable acid or (ii) a mixture of pharmaceutically acceptable acids in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of from about 10% to about 40% by weight of the total solution, (b) ethanol in the amount of from about 2% to about 8%, and (c) polyethylene glycol 540 in the amount of from about 25% to about 60% by weight of the total solution or saturated polyglycolized glyceride in the amount of from about 25% to about 60% by weight of the total solution.

20. The composition of claim 19 wherein the solution is encapsulated in a hard gelatin capsule.

21. The composition of claim 12 comprising a solution of (1) (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)-valinyl)amino)-2-(N-((5-thiazolyl)methoxy-

AUSTRALIAN PATENT OFFICE

carbonyl)amino)-1,6-diphenyl-3-hydroxyhexane in the amount of from about 20% to about 25% by weight of the total solution and (2) a total of about two molar equivalents (based on the compound of part (1)) of hydrochloric acid in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of from about 22% by weight of the total solution, (b) ethanol in the amount of from about 5% to about 6% by weight of the total solution, and (c) saturated polyglycolized glyceride in the amount of from about 30% to about 35% by weight of the total solution.

22. The composition of claim 21 wherein the solution is encapsulated in a hard gelatin capsule.

23. The composition of claim 12 comprising a solution of (1) (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane in the amount of from about 15% to about 20% by weight of the total solution and (2) a total of about two molar equivalents (based on the compound (1)) of a mixture of citric acid and hydrochloric acid in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of about 12% by weight of the total solution, (b) ethanol in the amount of from about 5% to about 6% by weight of the total solution, and (c) a saturated polyglycolized glyceride in the amount of from about 30% to about 35% by weight of the total solution.

24. The composition of claim 23 wherein the solution is encapsulated in a hard gelatin capsule.

25. The composition of claim 12 comprising a solution of (1) (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)-valinyl)amino)-2-(N-((5-thiazolyl)methoxy-carbonyl)amino)-1,6-diphenyl-3-hydroxyhexane in the amount of from about 15% to about 20% by weight of the total solution and (2) a total of about two molar equivalents (based on the compound (1)) of p-toluene-sulfonic acid in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of about 40% by weight of the total solution, (b) ethanol in the amount of from about 2% to about 3% by weight of the total solution, and (c) polyethylene glycol 540 in the amount of from about 30% to about 35% by weight of the total solution.

26. The composition of claim 25 wherein the solution is encapsulated in a hard gelatin capsule.

27. The composition of claim 12 comprising a solution of: (1) (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)-valinyl)amino)-2-(N-((5-thiazolyl)methoxy-carbonyl)amino)-1,6-diphenyl-3-hydroxyhexane in the amount of about 22% by weight of the total solution and (2) a total of about 1.6 molar equivalents (based on the compound (1)) of hydrochloric acid in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of about 20% by weight of the total solution, (b) ethanol in the amount of from about 5% to about 6% by weight of the total solution, and (c) a saturated polyglycolized glyceride in the amount of from about 30% to about 35% by weight of the total solution.

28. The composition of claim 27 wherein the solution is encapsulated in a hard gelatin capsule.

29. The composition of claim 12 comprising a solution of: (1) (2S,3S,5S)-5-(N-(N-((N-

AUSTRALIAN PATENT OFFICE

Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)-valinyl)amino)-2-(N-((5-thiazolyl)methoxy-carbonyl)amino)-1,6-diphenyl-3-hydroxyhexane in the amount of about 18% by weight of the total solution and (2) a total of about 0.5 molar equivalents (based on the compound (1)) of hydrochloric acid in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of about 12% by weight of the total solution, (b) ethanol in the amount of from about 5% to about 6% by weight of the total solution, and (c) a saturated polyglycolized glyceride in the amount of from about 30% to about 35% by weight of the total solution.

30. The composition of claim 29 wherein the solution is encapsulated in a hard gelatin capsule.

31. The composition of claim 12 comprising a solution of: (1) (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)-valinyl)amino)-2-(N-((5-thiazolyl)methoxy-carbonyl)amino)-1,6-diphenyl-3-hydroxyhexane in the amount of about 22% by weight of the total solution and (2) a total of about 1.8 molar equivalents (based on the compound (1)) of hydrochloric acid in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of about 20% by weight of the total solution, (b) ethanol in the amount of from about 5% to about 6% by weight of the total solution, and (c) a saturated polyglycolized glyceride in the amount of from about 30% to about 35% by weight of the total solution.

32. The composition of claim 31 wherein the solution is encapsulated in a hard gelatin capsule.

33. The composition of claim 12 comprising a solution of: (1) (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)-valinyl)amino)-2-(N-((5-thiazolyl)methoxy-carbonyl)amino)-1,6-diphenyl-3-hydroxyhexane in the amount of about 17% by weight of the total solution and (2) a total of about 0.4 molar equivalents (based on the compound (1)) of hydrochloric acid in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of about 14% by weight of the total solution, (b) ethanol in the amount of about 12% by weight of the total solution, and (c) a saturated polyglycolized glyceride in the amount of from about 30% to about 35% by weight of the total solution.

34. The composition of claim 33 wherein the solution is encapsulated in a hard gelatin capsule.

35. The composition of claim 12 comprising a solution of: (1) (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)-valinyl)amino)-2-(N-((5-thiazolyl)methoxy-carbonyl)amino)-1,6-diphenyl-3-hydroxyhexane in the amount of from about 15% to about 20% by weight of the total solution and (2) a total of from about 0.2 to about 0.8 molar equivalents (based on the compound (1)) of hydrochloric acid in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of from about 13% to about 14% by weight of the total solution, (b) ethanol in the amount of about 14% by weight of the total solution, and (c) a saturated polyglycolized glyceride in the amount of from about 30% to about 35% by weight of the total solution.

36. The composition of claim 35 wherein the solution is encapsulated in a hard gelatin capsule.

37. A solid pharmaceutical composition comprising a mixture of (A) a solution of (1)

RALIAN 340 OFFICE

(2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane in the amount of from about 4% to about 30% by weight of the total solution and (2) a total of from about 0.2 to about 2 molar equivalents (based on the compound of part (1)) of (i) a pharmaceutically acceptable acid or (ii) a mixture of pharmaceutically acceptable acids in a pharmaceutically acceptable organic solvent comprising a mixture of (a) a pharmaceutically acceptable alcohol or mixture of pharmaceutically acceptable alcohols in a total amount of from about 2% to about 50% by weight of the total solution, said alcohol or mixture of alcohols being a liquid at about room temperature and (b) a pharmaceutically acceptable solvent or a mixture of pharmaceutically acceptable solvents in a total amount of from about 20% to about 60% by weight of the total solution, said solvent or mixture of solvents having a melting point between about 20°C and about 60°C, said solvent or mixture of solvents being miscible with the alcohol or mixture of alcohols and providing a homogenous mixture with the alcohol or mixture of alcohols, said homogeneous mixture being a solid or semi-solid at about 20°C and (B) a pharmaceutically acceptable granulating agent or a mixture of pharmaceutically acceptable granulating agents.

38. The composition of claim 37 wherein the solid mixture is encapsulated in a hard gelatin capsule.

39. The composition of claim 37 comprising a mixture of (A) a solution of (1) (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane in the amount of from about 4% to about 30% by weight of the total solution and (2) a total of from about 0.2 to about 2 molar equivalents (based on the compound of part (1)) of (i) a pharmaceutically acceptable acid or (ii) a mixture of pharmaceutically acceptable acids in a pharmaceutically acceptable organic solvent comprising a mixture of (a) propylene glycol in the amount of from about 5% to about 40% by weight of the total solution, (b) ethanol in the amount of from about 2% to about 20%, and (c) polyethylene glycol 540 in the amount of from about 20% to about 60% or a total amount of from about 20% to about 60% by weight of the total solution of (i) a saturated polyglycolized glyceride or (ii) a mixture of saturated polyglycolized glycerides and (B) a pharmaceutically acceptable granulating agent or a mixture of pharmaceutically acceptable granulating agents.

40. The composition of claim 39 wherein the solid mixture is encapsulated in a hard gelatin capsule.

41. A pharmaceutical composition of (2S,3S,5S)-5-(N-(N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)-amino)carbonyl)-valinyl)amino)-2-(N-((5-thiazolyl)methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxyhexane, substantially as hereinbefore described with reference to any one of Examples 1-54.

Dated 2 July, 1998
Abbott Laboratories

Patent Attorneys for the Applicant/Nominated Person
SPRUSON & FERGUSON

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INTERNATIONAL SEARCH REPORT

Internatior \pplication No
PCT/US 94/09788

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/425 A61K38/55 A61K9/48 A61K47/02 A61K47/12 A61K47/10

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 6 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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X Y	EP,A,0 532 466 (CIBA-GEIGY AG) 17 March 1993 cited in the application see examples 28-32	1,2 3,4,41, 42
Y	US,A,5 206 219 (DESAI) 27 April 1993 see examples 1-4	3,4,41, 42
A	EP,A,0 486 948 (ABBOTT LABORATORIES) 27 May 1992 see page 142	1-42

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

Information on patent family members

Internatic Application No
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