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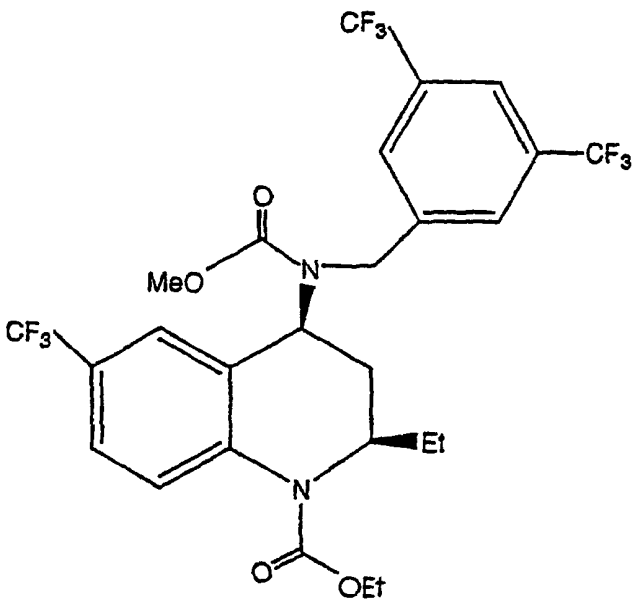
(54) Title: 4-CARBOXYAMINO-2-ETHYL-1,2,3,4-TETRAHYDROQUINOLINE CRYSTAL AS CETP INHIBITOR



(I)

(57) Abstract: Crystalline forms of a CETP inhibitor of formula (I), methods of making the crystals, methods of using the crystals and pharmaceutically compositions containing the crystals are disclosed.

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4-CARBOXYAMINO-2-ETHYL-1,2,3,4-TETRAHYDROQUINOLINE CRYSTAL AS CETP INHIBITOR

Background Of The Invention

This invention relates to cholesteryl ester transfer protein (CETP) inhibitors, pharmaceutical compositions containing such inhibitors and the use of such inhibitors to elevate certain plasma lipid levels, including high density lipoprotein (HDL)-cholesterol and to lower certain other plasma lipid levels, such as low density lipoprotein (LDL)-cholesterol and triglycerides and accordingly to treat diseases which are affected by low levels of HDL cholesterol and/or high levels of LDL-cholesterol and triglycerides, such as atherosclerosis and cardiovascular diseases in certain mammals (i.e., those which have CETP in their plasma), including humans.

More particularly, this invention relates to CETP inhibitor crystals, pharmaceutical compositions comprising these crystals, a process for preparing these crystals and to methods of treating atherosclerosis, obesity, and related diseases and/or conditions with the crystals.

Atherosclerosis and its associated coronary artery disease (CAD) is the leading cause of mortality in the industrialized world. Despite attempts to modify secondary risk factors (smoking, obesity, lack of exercise) and treatment of dyslipidemia with dietary modification and drug therapy, coronary heart disease (CHD) remains the most common cause of death in the U.S., where cardiovascular disease accounts for 44% of all deaths, with 53% of these associated with atherosclerotic coronary heart disease.

Risk for development of this condition has been shown to be strongly correlated with certain plasma lipid levels. While elevated LDL-cholesterol may be the most recognized form of dyslipidemia, it is by no means the only significant lipid associated contributor to CHD. Low HDL-cholesterol is also a known risk factor for CHD (Gordon, D.J., et al.,: "High-density Lipoprotein Cholesterol and Cardiovascular Disease", Circulation, (1989), 79: 8-15).

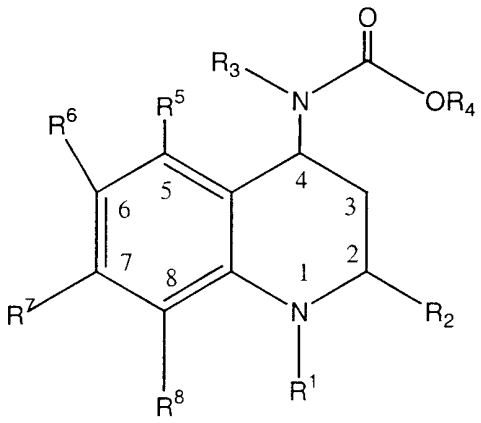
High LDL-cholesterol and triglyceride levels are positively correlated, while high levels of HDL-cholesterol are negatively correlated with the risk for developing cardiovascular diseases. Thus, dyslipidemia is not a unitary risk profile for CHD but may be comprised of one or more lipid aberrations.

Among the many factors controlling plasma levels of these disease dependent principles, cholesteryl ester transfer protein (CETP) activity affects all

three. The role of this 70,000 dalton plasma glycoprotein found in a number of animal species, including humans, is to transfer cholesteryl ester and triglyceride between lipoprotein particles, including high density lipoproteins (HDL), low density lipoproteins (LDL), very low density lipoproteins (VLDL), and chylomicrons. The net result of CETP activity is a lowering of HDL cholesterol and an increase in LDL cholesterol. This effect on lipoprotein profile is believed to be pro-atherogenic, especially in subjects whose lipid profile constitutes an increased risk for CHD.

No wholly satisfactory HDL-elevating therapies exist. Niacin can significantly increase HDL, but has serious toleration issues which reduce compliance. Fibrates and the HMG CoA reductase inhibitors raise HDL-C only modestly (~10-12%). As a result, there is a significant unmet medical need for a well-tolerated agent which can significantly elevate plasma HDL levels, thereby reversing or slowing the progression of atherosclerosis.

Commonly assigned U.S. application ser. No. 09/391,152 filed September 7, 1999 entitled 4-CARBOXYAMINO-2-SUBSTITUTED-1,2,3,4-TETRAHYDROQUINOLINES, the disclosure of which is hereby incorporated by reference, is directed to compounds of the following general formula:

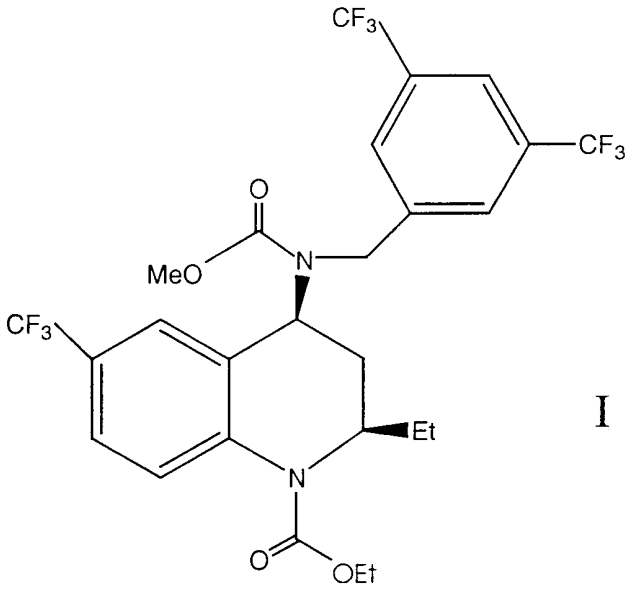


Specifically, the compound [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester is described.

Thus, although there are a variety of anti-atherosclerosis therapies, there is a continuing need and a continuing search in this field of art for alternative therapies.

Summary Of The Invention

This invention is directed to a Formula I crystal



I

Alternatively, a crystal of the above Formula I is named as [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester.

Another aspect of this invention is directed to an anhydrous crystal of Formula I.

Another aspect of this invention is directed to the corresponding anhydrous crystal having the X-ray powder diffraction pattern as shown in Figure 1.

Another aspect of this invention is directed to an ethanolate crystal of Formula I.

Another aspect of this invention is directed to the corresponding ethanolate crystal having the X-ray powder diffraction pattern as shown in Figure 2.

A preferred dosage is about 0.01 to 100 mg/kg/day of a Formula I crystal. An especially preferred dosage is about 0.1 to 10 mg/kg/day of a Formula I crystal.

In the text herein including the following methods, pharmaceutical compositions, combinations and kits reference is made to a crystal of Formula I. While it is understood that if the crystal is in solution, the crystal form is not present (in contrast to e.g., a dry tablet formulation), the following methods pharmaceutical compositions combinations and kits are intended to include a method or formulation

resulting from a use of such crystal (e.g., administering a gelatin capsule including an oil formulation solution of the crystal).

Yet another aspect of this invention is directed to methods for treating atherosclerosis, peripheral vascular disease, dyslipidemia, hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial-hypercholesterolemia, cardiovascular disorders, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, reperfusion injury, angioplastic restenosis, hypertension, vascular complications of diabetes, obesity or endotoxemia in a mammal (including a human being either male or female) by administering to a mammal in need of such treatment an atherosclerosis, peripheral vascular disease, dyslipidemia, hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial-hypercholesterolemia, cardiovascular disorders, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, reperfusion injury, angioplastic restenosis, hypertension, vascular complications of diabetes, obesity or endotoxemia treating amount of a Formula I crystal.

Yet another aspect of this invention is directed to a method for treating atherosclerosis in a mammal (including a human being) by administering to a mammal in need of such treatment an atherosclerosis treating amount of a Formula I crystal.

Yet another aspect of this invention is directed to a method for treating peripheral vascular disease in a mammal (including a human being) by administering to a mammal in need of such treatment a peripheral vascular disease treating amount of a Formula I crystal.

Yet another aspect of this invention is directed to a method for treating dyslipidemia in a mammal (including a human being) by administering to a mammal in need of such treatment a dyslipidemia treating amount of a Formula I crystal.

Yet another aspect of this invention is directed to a method for treating hyperbetalipoproteinemia in a mammal (including a human being) by administering to a mammal in need of such treatment a hyperbetalipoproteinemia treating amount of a Formula I crystal.

Yet another aspect of this invention is directed to a method for treating hypoalphalipoproteinemia in a mammal (including a human being) by administering to a mammal in need of such treatment a hypoalphalipoproteinemia treating amount of a Formula I crystal.

Yet another aspect of this invention is directed to a method for treating hypercholesterolemia in a mammal (including a human being) by administering to a mammal in need of such treatment a hypercholesterolemia treating amount of a Formula I crystal.

Yet another aspect of this invention is directed to a method for treating hypertriglyceridemia in a mammal (including a human being) by administering to a mammal in need of such treatment a hypertriglyceridemia treating amount of a Formula I crystal.

Yet another aspect of this invention is directed to a method for treating familial-hypercholesterolemia in a mammal (including a human being) by administering to a mammal in need of such treatment a familial-hypercholesterolemia treating amount of a Formula I crystal.

Yet another aspect of this invention is directed to a method for treating cardiovascular disorders in a mammal (including a human being) by administering to a mammal in need of such treatment a cardiovascular disorder treating amount of a Formula I crystal.

Yet another aspect of this invention is directed to a method for treating angina in a mammal (including a human being) by administering to a mammal in need of such treatment an angina treating amount of a Formula I crystal.

Yet another aspect of this invention is directed to a method for treating ischemia in a mammal (including a human being) by administering to a mammal in need of such treatment an ischemic disease treating amount of a Formula I crystal.

Yet another aspect of this invention is directed to a method for treating cardiac ischemia in a mammal (including a human being) by administering to a mammal in need of such treatment a cardiac ischemic treating amount of a Formula I crystal.

Yet another aspect of this invention is directed to a method for treating stroke in a mammal (including a human being) by administering to a mammal in need of such treatment a stroke treating amount of a Formula I crystal.

Yet another aspect of this invention is directed to a method for treating a myocardial infarction in a mammal (including a human being) by administering to a mammal in need of such treatment a myocardial infarction treating amount of a Formula I crystal.

Yet another aspect of this invention is directed to a method for treating reperfusion injury in a mammal (including a human being) by administering to a mammal in need of such treatment a reperfusion injury treating amount of a Formula I crystal.

Yet another aspect of this invention is directed to a method for treating angioplastic restenosis in a mammal (including a human being) by administering to a mammal in need of such treatment an angioplastic restenosis treating amount of a Formula I crystal.

Yet another aspect of this invention is directed to a method for treating hypertension in a mammal (including a human being) by administering to a mammal in need of such treatment a hypertension treating amount of a Formula I crystal.

Yet another aspect of this invention is directed to a method for treating the vascular complications of diabetes in a mammal (including a human being) by administering to a mammal in need of such treatment a vascular complications of diabetes treating amount of a Formula I crystal.

Yet another aspect of this invention is directed to a method for treating obesity in a mammal (including a human being) by administering to a mammal in need of such treatment an obesity treating amount of a Formula I crystal.

Yet another aspect of this invention is directed to a method for treating endotoxemia in a mammal (including a human being) by administering to a mammal in need of such treatment an endotoxemia treating amount of a Formula I crystal.

This invention is also directed to pharmaceutical compositions which comprise a therapeutically effective amount of a crystal of Formula I and a pharmaceutically acceptable carrier, vehicle or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of atherosclerosis, peripheral vascular disease, dyslipidemia, hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial-hypercholesterolemia, cardiovascular disorders, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, reperfusion injury, angioplastic restenosis, hypertension, vascular complications of diabetes, obesity or endotoxemia in a mammal (including a human being) which comprise a therapeutically effective amount of a crystal of Formula I and a pharmaceutically acceptable carrier, vehicle or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of atherosclerosis in a mammal (including a human being) which comprise an atherosclerosis treating amount of a crystal of Formula I and a pharmaceutically acceptable carrier, vehicle or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of peripheral vascular disease in a mammal (including a human being) which comprise a peripheral vascular disease treating amount of a crystal of Formula I and a pharmaceutically acceptable carrier, vehicle or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of dyslipidemia in a mammal (including a human being) which comprise a dyslipidemia treating amount of a crystal of Formula I and a pharmaceutically acceptable carrier, vehicle or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of hyperbetalipoproteinemia in a mammal (including a human being) which comprise a hyperbetalipoproteinemia treating amount of a crystal of Formula I and a pharmaceutically acceptable carrier, vehicle or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of hypoalphalipoproteinemia in a mammal (including a human being) which comprise a hypoalphalipoproteinemia treating amount of a crystal of Formula I and a pharmaceutically acceptable carrier, vehicle or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of hypercholesterolemia in a mammal (including a human being) which comprise a hypercholesterolemia treating amount of a crystal of Formula I and a pharmaceutically acceptable carrier, vehicle or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of hypertriglyceridemia in a mammal (including a human being) which comprise a hypertriglyceridemia treating amount of a crystal of Formula I and a pharmaceutically acceptable carrier, vehicle or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of familial-hypercholesterolemia in a mammal (including a human being) which comprise a familial-hypercholesterolemia treating amount of a crystal of Formula I and a pharmaceutically acceptable carrier, vehicle or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of angina in a mammal (including a human being) which comprise an

angina treating amount of a crystal of Formula I and a pharmaceutically acceptable carrier, vehicle or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of ischemia in a mammal (including a human being) which comprise an ischemic treating amount of a crystal of Formula I and a pharmaceutically acceptable carrier, vehicle or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of cardiac ischemia in a mammal (including a human being) which comprise a cardiac ischemic treating amount of a crystal of Formula I and a pharmaceutically acceptable carrier, vehicle or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of stroke in a mammal (including a human being) which comprise a stroke treating amount of a crystal of Formula I and a pharmaceutically acceptable carrier, vehicle or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of a myocardial infarction in a mammal (including a human being) which comprise a myocardial infarction treating amount of a crystal of Formula I and a pharmaceutically acceptable carrier, vehicle or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of reperfusion injury in a mammal (including a human being) which comprise a reperfusion injury treating amount of a crystal of Formula I and a pharmaceutically acceptable carrier, vehicle or diluent..

This invention is also directed to pharmaceutical compositions for the treatment of angioplastic restenosis in a mammal (including a human being) which comprise an angioplastic restenosis treating amount of a crystal of Formula I and a pharmaceutically acceptable carrier, vehicle or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of hypertension in a mammal (including a human being) which comprise a hypertension treating amount of a crystal of Formula I and a pharmaceutically acceptable carrier, vehicle or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of the vascular complications of diabetes in a mammal (including a human being) which comprise a vascular complications of diabetes treating amount of a crystal of Formula I and a pharmaceutically acceptable carrier, vehicle or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of obesity in a mammal (including a human being) which comprise an obesity treating amount of a crystal of Formula I and a pharmaceutically acceptable carrier, vehicle or diluent.

This invention is also directed to pharmaceutical compositions for the treatment of endotoxemia in a mammal (including a human being) which comprise an endotoxemia treating amount of a crystal of Formula I and a pharmaceutically acceptable carrier, vehicle or diluent.

This invention is also directed to a pharmaceutical combination composition comprising: a therapeutically effective amount of a composition comprising

a first compound, said first compound being a Formula I crystal;

a second compound, said second compound being an HMG-CoA reductase inhibitor, an microsomal triglyceride transfer protein (MTP)/Apo B secretion inhibitor, a PPAR activator, a bile acid reuptake inhibitor, a cholesterol absorption inhibitor, a cholesterol synthesis inhibitor, a fibrate, niacin, an ion-exchange resin, an antioxidant, an ACAT inhibitor or a bile acid sequestrant; and/or optionally

a pharmaceutical carrier, vehicle or diluent.

Preferred among the second compounds are an HMG-CoA reductase inhibitor and a MTP/Apo B secretion inhibitor.

A particularly preferred HMG-CoA reductase inhibitor is lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin or rivastatin.

Another aspect of this invention is a method for treating atherosclerosis in a mammal comprising administering to a mammal suffering from atherosclerosis

a first compound, said first compound being a Formula I crystal; and

a second compound, said second compound being an HMG-CoA reductase inhibitor, an MTP/Apo B secretion inhibitor, a cholesterol absorption inhibitor, a cholesterol synthesis inhibitor, a fibrate, niacin, an ion-exchange resin, an antioxidant, an ACAT inhibitor or a bile acid sequestrant wherein the amounts of the first and second compounds result in a therapeutic effect.

A preferred aspect of the above method is wherein the second compound is an HMG-CoA reductase inhibitor or an MTP/Apo B secretion inhibitor.

A particularly preferred aspect of the above method is wherein the HMG-CoA reductase inhibitor is lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin or rivastatin.

Yet another aspect of this invention is a kit comprising:

a. a first compound, said first compound being a Formula I crystal, and a pharmaceutically acceptable carrier in a first in a unit dosage form;

b. a second compound, said second compound being an HMG CoA reductase inhibitor, an MTP/Apo B secretion inhibitor, a cholesterol absorption inhibitor, a cholesterol synthesis inhibitor, a fibrate, niacin, an ion-exchange resin, an antioxidant, an ACAT inhibitor or a bile acid sequestrant and a pharmaceutically acceptable carrier in a second unit dosage form; and

c. means for containing said first and second dosage forms wherein the amounts of the first and second compounds result in a therapeutic effect.

A preferred second compound is an HMG-CoA reductase inhibitor or an MTP/Apo B secretion inhibitor.

A particularly preferred HMG-CoA reductase inhibitor is lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin or rivastatin.

The present invention is also directed to processes for preparing crystalline anhydrous [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester by dissolving or mixing [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester in the presence of a suitable organic solvent, preferably hexanes.

Another aspect of this invention is directed to a process for preparing crystalline ethanolate [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester by dissolving or mixing [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester in ethanol/water at ambient temperature for about 0.5 to about 18 hours. Preferably ethanol is used without water.

This invention is also directed to a process for preparing crystalline anhydrous [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester comprising dissolving or mixing [2R,4S] 4-[3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester in ethanol at ambient temperature for about 2 to about 24 hours.

It is noted that as the anhydrous and ethanolate crystals are of different energy levels seeding with either anhydrous or ethanolate may determine the resulting isolated crystalline form. As is known in the art the presence of seed crystals in the air in a lab may be sufficient "seeding." In one embodiment anhydrous crystals may be obtained using hexanes and the resulting anhydrous crystals may be used to seed the production of further anhydrous crystals from ethanol.

As used herein the term mammals is meant to refer to all mammals which contain CETP in their plasma, for example, rabbits and primates such as monkeys and humans. Certain other mammals e.g., dogs, cats, cattle, goats, sheep and horses do not contain CETP in their plasma and so are not included herein.

The term ethanolate refers to an ethanol of solvation.

The term "treating", "treat" or "treatment" as used herein includes preventative (e.g., prophylactic) and palliative treatment.

By "pharmaceutically acceptable" it is meant the carrier, vehicle, diluent, excipients, and/or salt must be compatible with the other ingredients of the formulation, and not deleterious to the recipient thereof.

As used herein, the expressions "reaction-inert solvent" and "inert solvent" refers to a solvent or mixture of solvents which does not interact with starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product.

It will be recognized that the compound of this invention can exist in radiolabelled form, i.e., said compound may contain one or more atoms containing an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Radioisotopes of hydrogen, carbon, phosphorous, fluorine and chlorine include ^{3}H, ^{14}C, ^{32}P, ^{35}S, ^{18}F and ^{36}Cl, respectively. The compound of this invention which contains those radioisotopes and/or other radioisotopes of other atoms is within the scope of this invention. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, radioisotopes are particularly preferred for their ease of preparation and detectability. A radiolabelled compound of this invention can generally be prepared by methods well known to those skilled in the art. Conveniently, such radiolabelled compounds can be prepared by carrying out the procedures disclosed in the Examples below by substituting a readily available radiolabelled reagent for a non-radiolabelled reagent.

Other features and advantages will be apparent from the specification and claims which describe the invention.

Brief Description of the Drawings

FIG. 1 is a characteristic x-ray powder diffraction pattern showing that anhydrous [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester is crystalline. (Vertical Axis: Intensity (CPS); Horizontal Axis: Two theta (degrees))

FIG. 2 is the characteristic x-ray powder diffraction pattern of the ethanolate [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester as crystalline Vertical Axis: Intensity (CPS); Horizontal Axis: Two theta (degrees))

Detailed Description Of The Invention

In general the compound of this invention can be made by processes which include analogous processes known in the chemical arts, particularly in light of the description contained herein. Certain processes for the manufacture of the compound of this invention are provided as further features of the invention and are described below including in the Examples.

The amorphous form of the compound of this invention [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester is prepared as disclosed below (see Example 1).

An anhydrous crystalline form of the above compound may be prepared from the amorphous compound by recrystallization from hexanes (solvent comprised of hexane isomers (e.g., n-hexane, cyclohexane, methyl pentane, etc.)) at a temperature of about 40°C to about 80°C, preferably 60° followed typically by granulating, for about 2 to about 24 hours, then filtering the material and subsequent air drying.

Alternatively, the anhydrous crystal may be prepared from the ethanolate crystalline form (described below) utilizing analogous procedures to the immediately preceding procedure. In addition, the yield in this procedure may be enhanced by azeotroping the ethanol from the hexanes.

An ethanolate crystalline form of the above compound may be prepared from the amorphous compound by recrystallization from ethanol/water at a temperature of about 20°C to about 25°C, preferably ambient temperature for about 0.5 hour to about 18 hours. Typically the range is about 3% to about 10% ethanol and about

90% to about 97% water. Preferably the ratio is about 10% to about 90% ethanol/water.

Alternatively, the ethanolate crystalline form may be prepared utilizing procedures analogous to those described above but using ethanol alone. The filtered materials are typically granulated for about 2 hours to about 24 hours followed by air drying.

The following Table 1 details important properties for three forms of [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester: the amorphous (A); and the two crystalline forms ethanolate (B) and crystalline anhydrous (C).

TABLE 1

	Thermal Stability	Crystallinity	Solubility	Stability
Amorphous A	M.P. 21°C	Non-crystalline	Most soluble in aqueous	hygrocopic
[1]Ethanolate B (Fig. 2)	Melt onset 45°C	Crystalline	Higher solubility in aqueous than Anhydrous (C)	non-hygroscopic @ 90% relative humidity over 24 hours
Anhydrous C (Fig. 1)	M.P. 89-90°C	Crystalline	Least soluble in water	non-hygroscopic at 80% & 100% relative humidity over 3 days.

[1]Loses some ethanol at closed bottle ambient conditions but remains crystalline

The compound of the instant invention is orally administrable and is accordingly used in combination with a pharmaceutically acceptable vehicle, carrier or diluent suitable to oral dosage forms. Suitable pharmaceutically-acceptable carriers include inert solid fillers or diluents and sterile aqueous or organic solutions. The active compound will be present in such pharmaceutical compositions in amounts sufficient to provide the desired dosage amount in the range described below. Thus, for oral administration the compound may be combined with a suitable solid or liquid carrier or diluent to form capsules, tablets, powders, syrups, solutions, suspensions and the like. The pharmaceutical compositions may, if desired, contain additional components such as flavorants, sweeteners, excipients and the like.

The tablets, pills, capsules, and the like may also contain a binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin. When a dosage unit form is a capsule, for example a gel capsule, it may contain, in addition to or instead of materials of the above type, a liquid carrier such as a fatty glyceride or mixtures of fatty glycerides, such as olive oil, or Miglyol™ or Capmul™ glycerides. Dosage forms may also include orral suspensions.

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a

sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

The compound of the instant invention may also be administered parenterally. For parenteral administration the compound may be combined with sterile aqueous or organic media to form injectable solutions or suspensions. The injectable solutions prepared in this manner can then be administered intravenously, intraperitoneally, subcutaneously, or intramuscularly.

The pharmaceutical forms suitable for injectable use include sterile solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. They may be sterilized, for example, by filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the compositions, or by irradiating or heating the compositions where such irradiating or heating is both appropriate and compatible with the drug formulation.

Additional pharmaceutical formulations may include, inter alia, suppositories, sublingual tablets, topical dosage forms and the like and these may be prepared according to methods which are commonly accepted in the art.

Controlled release, sustained release, and delayed release oral or parenteral compositions may be used.

The dosage of the compound of the instant invention which is administered will generally be varied according to principles well known in the art taking into account the severity of the condition being treated and the route of administration. In general, the compound will be administered to a warm blooded animal (such as a human, livestock or pet) so that an effective dose, usually a daily dose administered in unitary or divided portions, is received, for example a dose in the range of about 0.01 to about 100 mg/kg/day body weight, preferably about 0.1 to about 10 mg/kg/day body weight. The above dosages are exemplary of the average case; there can, of course, be individual instances where higher or lower dosage ranges are merited, and such deviations are within the scope of this invention.

EXAMPLES

Melting points were determined with a Thomas Hoover melting point apparatus or a DSC apparatus. Unless otherwise stated, CD_3Cl_3 was used for NMR

spectra. Microanalysis was performed by Schwarzkopf Microanalytical Laboratory. All reagents and solvents were obtained commercially and used without purification.

Example 1

cis-4-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester:

A solution of *cis*-4-(3,5-bis-trifluoromethyl-benzylamino)-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (2.0 g, 3.7 mmol) and pyridine (0.58 g, 7.4 mmol) in 100 mL of dichloromethane was cooled in an ice/water bath as methyl chloroformate (0.87 g, 9.2 mmol) was added slowly. After stirring overnight at room temperature, the reaction mixture was washed twice with a 2N hydrochloric acid solution, dried over magnesium sulfate, filtered and concentrated *in vacuo* to afford the crude product, which was purified by silica gel chromatography using 5-10% ethyl acetate/hexanes as eluent to afford 1.8 g of the title product. MS *m/z* 601 ($M^+ + 1$); ^{1}H NMR (coalescing mixture of conformers, $CDCl_3$) δ 0.6-0.8 (bm, 3H), 1.2-1.3 (bm, 3H), 1.3-1.5 (bm, 2H), 1.6-1.75 (bm, 1H), 2.1-2.3 (bm, 1H), 3.7-3.9 (bs, 3H), 4.0-4.4 (bm, 4H), 5.0-5.6 (bm, 2H), 7.1 (s, 1H), 7.4-7.6 (bm, 2H), 7.6-7.8 (bm, 3H).

[2R,4S]4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester was prepared in optically enriched form by resolution of the corresponding racemate, or an intermediate in its synthesis, using standard methods.

Example 2

(1-Benzotriazol-1-yl-propyl)-(4-trifluoromethyl-phenyl)-amine

A two liter, four neck flask under nitrogen atmosphere was charged with benzotriazole (36.96 g, 310 mmol, 1.0 equiv) and dry toluene (400 mL). A room temperature solution of 4-(trifluoromethyl)aniline (39.1 mL, 310 mmol, 1.0 equiv) and 50 mL toluene was added over one minute. A room temperature solution of propionaldehyde (24.6 mL, 341 mmol, 1.1 equiv) and 50 mL toluene was then added over 20 minutes. There was an exotherm from 23°C to 30°C during this addition. After stirring 24 h, n-heptane (500 mL) was added, and the slurry stirred an additional 1 h. The suspension was filtered, the solids were washed with n-heptane (1 x 100 mL, then 1 x 200 mL, and dried. (1-Benzotriazol-1-yl-propyl)-(4-trifluoromethyl-phenyl)-amine was isolated as shiny white needles (81.3 g, 82%). After 24 h, a second crop was isolated from the filtrate (8.7 g, 9%). mp 130-132 °C; ^{1}H NMR

(DMSO-d6, 400 MHz) δ 0.82 (t, 3H, J=7.5 Hz), 2.25 (m, 2H), 6.49 (m, 1H), 6.80 (d, 2H, J=8.7 Hz), 7.35 (m, 3H), 7.50 (m, 1H), 7.88 (d, 1H, J=8.3 Hz), 7.99 (m, 1H), 8.09 (d, 1H, J=8.5 Hz); ^{13}C NMR (DMSO-d6, 100 MHz) δ 149.32, 146.19, 131.46, 127.73, 126.8, 125.33 (q, J=270 Hz), 124.44, 119.88, 118.27 (q, J=31.7 Hz), 112.91, 111.56, 71.03, 28.08, 10.29; DEPT spectrum: quaternary carbons δ 149.32, 146.19, 131.46, 125.33, 118.27; CH carbons δ 127.73, 126.8, 124.44, 119.88, 112.91, 111.56, 71.03; CH_2 carbon δ 28.08; CH_3 carbon δ 10.29; IR (drifts) 3292 (s), 3038 (m), 2975 (m), 1621 (s), 1331 (s), 1320 (s), 1114 (vs); Anal. Calcd for $C_{16}H_{15}N_4F_3$: C, 59.99; H, 4.72; N, 17.49. Found (first crop): C, 60.16; H, 4.74; N, 17.86. Found (second crop): C, 59.97; H, 4.66; N, 17.63.

Example 3

cis-(2-Ethyl-6-trifluoromethyl-1,2,3,4-tetrahydro-quinolin-4-yl)-carbamic acid benzyl ester

A one liter, four neck flask under nitrogen atmosphere was charged with N-vinyl-carbamic acid benzyl ester (27.66 g, 156 mmol, 1.0 equiv) and dry toluene (500 mL). (1-Benzotriazol-1-yl-propyl)-(4-trifluoromethyl-phenyl)-amine (50.0 g, 156 mmol, 1.0 equiv) and *p*-toluenesulfonic acid monohydrate (297 mg, 1.56 mmol, 0.01 equiv) were added, and the mixture heated to 70°C. After 2 h, the mixture was cooled to room temperature and transfered to a separatory funnel. Ethyl acetate (500 mL) was added. The mixture was washed 1 x 200 mL 1N NaOH, 1 x 200 mL H_2O, 1 x 200 mL brine, and dried ($MgSO_4$). The mixture was filtered and the solids washed 1 x 50 mL ethyl acetate. The filtrate was concentrated to approximately 250 mL. 500 mL toluene were added, and the mixture concentrated to approximately 500 mL. 500 mL n-heptane were added, the slurry was stirred 1 h, filtered through a Buchner funnel, and dried. cis-(2-Ethyl-6-trifluoromethyl-1,2,3,4-tetrahydro-quinolin-4-yl)-carbamic acid benzyl ester was isolated as a white powder (45.04 g, 76%): mp 155-157 °C; ^{1}H NMR (DMSO-d6, 400 MHz) δ 0.92 (t, 3H, J=7.5 Hz), 1.5 (m, 3H), 2.00 (m, 1H), 3.35 (m, 1H), 4.77 (m, 1H), 5.07 (d, 1H, J=12.5 Hz), 5.15 (d, 1H, J=12.5 Hz), 6.35 (s, 1H), 6.61 (d, 1H, J=8.5 Hz), 7.12 (s, 1H), 7.18 (dd, 1H, J=1.9, 8.5 Hz), 7.4 (m, 5H), 7.70 (d, 1H, J=9.1 Hz); ^{13}C NMR (DMSO-d6, 100 MHz) δ 157.03, 149.02, 137.79, 128.82, 128.23, 128.03, 125.9 (q, J=270 Hz), 125.06, 123.50, 121.73, 115.2 (q, J=31.7 Hz), 113.33, 65.85, 52.09, 47.83, 34.02, 28.68, 9.93; DEPT spectrum: quaternary carbons δ 157.03, 149.02, 137.79, 125.9, 121.73, 115.2; CH carbons δ 128.82,

128.23, 128.03, 125.06, 123.50, 113.33, 52.09, 47.83; CH_2 carbons δ 65.85, 34.02, 28.68; CH_3 carbon δ 9.93; IR (drifts) 3430 (m), 3303 (s), 2951 (m), 1686 (vs), 1542 (vs), 1088 (vs); MS (APCI+) m/z (rel. intensity) 379 ($M+H^+$, 53), 228 (100); Anal. Calcd for $C_{20}H_{21}N_2O_2F_3$: C, 63.48; H, 5.59; N, 7.40; Found: C, 63.69; H, 6.06, N, 7.36.

Example 4

cis-4-Benzyloxycarbonylamino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester

A three liter, four neck flask under nitrogen atmosphere was charged with cis-(2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydro-quinolin-4-yl)-carbamic acid benzyl ester (96.0 g, 254 mmol, 1.0 equiv), dry dichloromethane (720 mL), and dry pyridine (103 mL, 1.27 mol, 5.0 equiv). A solution of ethyl chloroformate (121 mL, 1.27 mol, 5.0 equiv), in dry dichloromethane (240 mL), was added slowly over 4 h. The addition was exothermic and required a reflux condenser. Once the chloroformate addition was complete, the reaction was cooled in an ice bath and 1350 mL 1N NaOH were added. The mixture was stirred 15 min, then transferred to a separatory funnel. The layers were separated and the aqueous extracted 1 x 1L dichloromethane. The combined dichloromethane layers were washed 1 x 1350 mL 1N HCl, 1 x 1L saturated aq. $NaHCO_3$, 1 x 1L brine, and dried (Na_2SO_4). The mixture was filtered, and the filtrate concentrated to an orange oil. 570 mL abs. ethanol were added, and the solution was concentrated. The solids were dissolved in 1370 mL abs. ethanol. 570 mL H_2O were added dropwise over 45 min. The resultant thick slurry was stirred 18 h and filtered. The solids were washed with cold 7:3 abs. ethanol/water (1 x 250 mL, then 1 x 100 mL) and dried (vac oven, 45°C) to give cis-4-benzyloxycarbonylamino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester as a white, crystalline solid (94.54 g, 83%): mp 92-96°C; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.84 (t, 3H, J=7.4 Hz), 1.28 (t, 3H, J=7.0 Hz), 1.4 (m, 2H), 1.62 (m, 1H), 2.53 (m, 1H), 4.23 (m, 2H), 4.47 (m, 1H), 4.79 (m, 1H), 5.01 (d, 1H, J=9.2 Hz), 5.18 (m, 2H), 7.4 (m, 5H), 7.5 (m, 2H), 7.57 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.97, 154.43, 139.44, 136.21, 134.33, 128.61, 128.33, 128.22, 126.32 (q, J=31.7 Hz), 126.18, 124.22, 124.19, 124.12 (q, J=273 Hz), 120.74, 120.70, 67.22, 62.24, 53.47, 46.79, 37.75, 28.25, 14.38, 9.78; DEPT spectrum: quaternary carbons δ 155.97, 154.43, 139.44, 136.21, 134.33, 126.32, 124.12; CH carbons δ 128.61,

128.33, 128.22, 126.18, 124.22, 124.19, 120.74, 120.70, 53.47, 46.79; CH_2 carbons δ 67.22, 62.24, 37.75, 28.25; CH_3 carbons δ 14.38, 9.78; IR (drifts) 3304 (s), 3067 (m), 3033 (m), 2982 (m), 2932 (m), 1723 (s), 1693 (s), 1545 (s); MS (APCI+) m/z (rel. intensity) 451 ($M+H^+$, 2), 300 (100); Anal. Calcd for $C_{23}H_{25}N_2O_4F_3$: C, 61.33; H, 5.60; N, 6.22. Found: C, 61.07; H, 5.69; N, 6.22.

Example 5

cis-4-Amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester

A one liter, four neck flask under nitrogen atmosphere was charged with cis-4-benzyloxycarbonylamino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (40.1 g, 89 mmol, 1.0 equiv), methanol (400 mL), and ammonium formate (14.0 g, 223 mmol, 2.5 equiv). 10% Pd/C, 50% water wet (4.0 g) was added, and the slurry heated to 40° C over 1 h. After 1.5 h, the mixture was cooled to room temperature and filtered through Celite®. The cake was washed 2 x 100 mL methanol. The filtrate was concentrated to approximately 75 mL, transferred to a separatory funnel, and diluted with 400 mL ethyl acetate. The mixture was washed 1 x 125 mL saturated aq. $NaHCO_3$, 1 x 100 mL brine, and dried (Na_2SO_4). The mixture was filtered and the filtrate concentrated to a clear oil. The oil was crystallized from 100 mL n-heptane to give cis-4-amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester as a white crystalline solid (26.05 g, 93%): mp 61.5-63.5° C; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.79 (t, 3H, J=7.5 Hz), 1.24 (m, 4H), 1.42 (m, 1H), 1.51 (br s, 2H), 1.62 (m, 1H), 2.46 (m, 1H), 3.73 (m, 1H), 4.17 (m, 2H), 4.36 (m, 1H), 7.44 (m, 2H), 7.66 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.6, 139.3, 138.9, 126.3 (q, J=32 Hz), 125.7, 124.3 (q, J=271 Hz), 123.5, 119.8, 61.96, 54.16, 46.91, 41.50, 28.85, 14.38, 9.60; DEPT spectrum: quaternary carbons δ 154.6, 139.3, 138.9, 126.3, 124.3; CH carbons δ 125.7, 123.5, 119.8, 54.16, 46.91; CH_2 carbons δ 61.96, 41.50, 28.85; CH_3 carbons δ 14.38, 9.60; IR (drifts) 3350 (s), 3293 (m), 2972 (s), 1697 (vs); MS (ES+) m/z (rel. intensity) 358 ($M+H+CH_3CN^+$, 55), 317 ($M+H^+$, 7), 300 (100); Anal. Calcd for $C_{15}H_{19}N_2O_2F_3$: C, 56.96; H, 6.06; N, 8.86. Found: C, 56.86; H, 6.28; N, 8.82.

Example 6

(-) (2R, 4S)-4-Amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester hemi-(-)-dibenzoyl-L-tartrate salt

A one liter flask under nitrogen atmosphere was charged with cis-4-benzyloxycarbonylamino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (24.0 g, 75.9 mmol, 1.0 equiv) and (-) dibenzoyl-L-tartaric acid (anhydrous) (27.19 g, 75.9 mmol, 1.0 equiv). 300 mL of approximately 97% ethanol (prepared by adding 10.5 mL H_2O to 500 mL absolute ethanol, mixing, and measuring out 300 mL) was added. The mixture was stirred at room temperature for 18 h, then filtered. The solids were washed 1 x 48 mL approximately 97% ethanol, and dried to give (-) (2R, 4S)-4-amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester hemi-(-)-dibenzoyl-L-tartrate salt as a white crystalline solid (14.77 g, 39%): mp 189.5-191.5 °C (dec); ^{1}H NMR (DMSO-d6, 400 MHz) δ 0.62 (t, 3H, J=7.3 Hz), 1.16 (t, 3H, J=7.1Hz), 1.3 (m, 3H), 2.5 (m, 1H), 4.1 (m, 4H), 5.63 (s, 1H, methine proton in DBTA), 7.47 (m, 2H, DBTA aromatic H's), 7.6 (m, 3H, DBTA aromatic H's), 7.68 (s, 1H), 7.95 (m, 2H), 8.2 (br s, NH_3^+, did not integrate); ^{13}C NMR (DMSO-d6, 100 MHz) δ 169.85, 165.53, 154.10, 140.14, 134.59, 133.51, 130.74, 129.69, 128.98, 126.74, 124.82 (q, J=31.7 Hz), 124.69 (q, J=271 Hz), 124.50, 120.90, 74.49, 62.14, 53.51, 45.94, 38.81, 28.23, 14.63, 9.58; DEPT spectrum: quaternary carbons δ 169.85, 165.53, 154.10, 140.14, 134.59, 130.74, 124.82, 124.69; CH carbons δ 133.51, 129.69, 128.98, 126.74, 124.50, 120.90, 74.49, 53.51, 45.94; CH_2 carbons δ 62.14, 38.81, 28.23; CH_3 carbons δ 14.63, 9.58; IR (drifts) 3278 (m), 2400-3100 (broad), 1703 (vs); MS (ES+) m/z (rel. intensity) 358 ($M+H+CH_3CN^+$, 55), 317 ($M+H^+$, 7), 300 (100); Anal. Calcd for $C_{15}H_{19}N_2O_2F_3.C_9H_7O_4$: C, 58.18; H, 5.29; N, 5.65. Found: C, 57.99; H, 5.15; N, 5.64; Chiral HPLC: mobile phase 950:50:2 n-hexane:2-propanol:HOAc, flow rate 1.50 mL/min, column temp 40°C, chiralpak™ AD 4.6 x 250 mm, sample concentration approximately 0.5 mg/mL in approximately 1:1 n-hexane:2-propanol. Authentic racemate shows retention times of 7.5 min and 10.0 min. (-) (2R, 4S)-4-Amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester hemi-(-)-dibenzoyl-L-tartrate salt: 10.0 min, 88.9%, 7.5 min <<1%, 2.0 min (solvent front) 11.1%; $[\alpha]_D$ = -153 (c=1.07, CH_3OH).

Example 7

<u>(-)-(2R, 4S)-4-(3,5-Bis-trifluoromethyl-benzylamino)-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester tosylate salt</u>

(-) (2R, 4S)-4-Amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester hemi-(-)-dibenzoyl-L-tartrate salt (13.0 g, 26.2 mmol, 1.0 equiv) was

suspended in 1,2-dichloroethane (260 mL) in a 500 mL separatory funnel. The mixture was washed 1 x 65 mL 1N NaOH, 1 x 65 mL brine, and dried ($MgSO_4$). The mixture was filtered, concentrated to approximately approximately 80 mL, and transferred to a 250 mL three neck flask. 3,5-Bis(trifluoromethyl)benzaldehyde (4.53 mL, 27.5 mmol, 1.05 equiv) was added, and the mixture stirred 1 h at room temperature under nitrogen atmosphere. Sodium triacetoxyborohydride (11.1 g, 52.4 mmol, 2.0 equiv) was added in one portion, and the white slurry was stirred 18 h. 50 mL 1,2-dichloroethane and 50 mL 2N NaOH were added, and the aqueous layer extracted 2 x 50 mL 1,2-dichloroethane. The combined organic extracts were washed 1 x 31 mL 1N HCl, 1 x 50 mL saturated aq. $NaHCO_3$, 1 x 50 mL brine, and dried (Na_2SO_4). The mixture was filtered and concentrated to a clear oil. The oil was dissolved in methanol (71 mL). *p*-Toluenesulfonic acid monohydrate (5.23 g, 27.5 mmol, 1.05 equiv) was added. After 5 min, 284 mL isopropyl ether was added. The solution was concentrtated to approximately 35mL, transferred to a 500 mL three neck flask (mech. stirrer), and diluted with 284 mL isopropyl ether. A thick white slurry formed in 10 minutes. After stirring 3 h, the slurry was filtered and the cake washed 2 x 70 mL isopropyl ether. After drying, (-)-(2R, 4S)-4-(3,5-bis-trifluoromethyl-benzylamino)-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester tosylate salt was isolated as a white powder (16.18 g, 86% overall): mp 191-192°C; ^{1}H NMR (DMSO-d6, 400 MHz) δ 0.78 (t, 3H, J=7.5 Hz), 1.21 (t, 3H, J=7.0 Hz), 1.5 (m, 3H), 2.24 (s, 3H), 3.08 (m, 1H), 4.17 (m, 2H), 4.41 (m, 1H), 4.50 (m, 2H), 4.79 (m, 1H), 7.04 (d, 2H, J=7.9 Hz), 7.42 (d, 2H, J=7.9 Hz), 7.7 (m, 2H), 7.81 (s, 1H), 8.21 (s, 1H), 8.35 (s, 2H), 9.58 (br s, 1H), 9.83 (br s, 1H); ^{13}C NMR (DMSO-d6, 100 MHz) δ 154.00, 145.46, 140.21, 138.39, 135.33, 132.51, 131.62, 130.79 (q, J=33.2 Hz), 128.49, 127.40, 125.82, 125.36, 124.99 (q, J=31.7 Hz), 124.59 (q, J=271 Hz), 123.69 (q, J=273 Hz), 123.44, 120.33, 62.32, 53.99, 53.79, 47.98, 33.30, 28.61, 21.13, 14.63, 9.58; DEPT spectrum: quaternary carbons δ 154.00, 145.46, 140.21, 138.39, 135.33, 130.79, 124.99, 124.59, 123.69; CH carbons δ 132.51, 131.62, 128.49, 127.40, 125.82, 125.36, 123.44, 120.33, 53.99, 53.79; CH_2 carbons δ 62.32, 47.98, 33.30, 28.61; CH_3 carbons δ 21.13, 14.63, 9.58: IR (drifts) 2300-3100 (broad), 2974 (m), 2731 (m), 2620 (m), 2455 (m), 1714 (s), 1621 (m), 1283 (vs), 1169 (vs), 1126 (vs); MS (ES+) m/z (rel. intensity) 584 ($M+H+CH_3CN^+$, 100), 543 ($M+H^+$, 80); Anal. Calcd for $C_{24}H_{23}N_2O_2F_9.C_7H_8O_3S$: C, 52.11; H, 4.37; N,

3.92. Found: C, 52.15; H, 4.22; N, 3.69; $[\alpha]_D$ = -77.9 (c = 1.05, CH_3OH).

Example 8

(-)-(2R, 4S)-4-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester mono ethanolate

Na_2CO_3 (s) (6.75 g, 63.7 mmol, 3.5 equiv) was added to a room temperature solution of (-)-(2R, 4S)-4-(3,5-bis-trifluoromethyl-benzylamino)-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester tosylate salt (13.0 g, 18.2 mmol, 1.0 equiv) in dry THF (130 mL). Methyl chloroformate (3.51 mL, 45.5 mmol, 2.5 equiv) was added neat, dropwise over 2 min. After 24 h, the mixture was concentrated to 65 mL, diluted with 260 mL ethyl acetate, and transferred to a separatory funnel. The mixture was washed 1 x 90 mL 1N HCl (CO_2 evolution), 1 x 90 mL saturated aq. $NaHCO_3$, 1 x 90 mL brine, and dried ($MgSO_4$). Filtration and concentration of filtrate afforded a clear oil, which was costripped 3 x 33 mL 2B ethanol. The oil was dissolved in 33 mL 2B ethanol and seeded with a few milligrams of (-)-(2R, 4S)-4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester mono ethanolate. After stirring 18 h at room temperature, the slurry was filtered and dried to give (-)-(2R, 4S)-4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester mono ethanolate as a white crystalline powder (8.66 g, 74%): mp 54-58 °C; ^{1}H NMR ($CDCl_3$, 400 MHz, 55°C) δ 0.73 (t, 3H, J=7.0 Hz), 1.20 (t, EtOH), 1.27 (t, 3H, J=7.1 Hz), 1.42 (m, 2H), 1.66 (m, 1H), 2.25 (br s, 1H), 3.67 (q, EtOH), 3.79 (s, 3H), 4.2 (m, 3H), 4.33 (m, 1H), 5.2 (br s, 2H), 7.12 (s, 1H), 7.49 (d, 1H, J=8.3 Hz), 7.57 (d, 1H, J=8.5 Hz), 7.73 (s, 2H), 7.78 (s, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 157.74, 154.37, 141.73, 140.05, 133.83, 132.14 (q, J=33 Hz), 126.94, 124.49, 123.96 (q, J=273 Hz), 123.13 (q, J=273 Hz), 121.31, 119.17, 62.29, 58.28, 54.42, 53.71, 53.08, 46.67, 37.01, 29.02, 18.29, 14.32, 9.22, (note: the fourth quartet appears to be buried under the δ 126.94 peak, with J approximately 32 Hz); DEPT spectrum: quaternary carbons δ 157.74, 154.37, 141.73, 140.05, 133.83, 132.14, 123.96, 123.13; CH carbons δ 126.94, 124.49, 121.31, 119.17, 54.42, 53.08; CH_2 carbons δ 62.29, 58.28, 46.67, 37.01, 29.02; CH_3 carbons δ 53.71, 18.29, 14.32, 9.22; IR (drifts) 3489 (s), 2974 (s), 2884 (m), 1701 (vs), 1280 (vs), 1131 (vs); MS (ES+) m/z (rel. intensity) 601 ($M+H^+$, 100); Anal. Calcd for $C_{26}H_{25}N_2O_4F_9.C_2H_6O$: C, 52.01; H, 4.83; N, 4.33. Found: C,

51.84; H, 4.54; N, 4.33; chiral HPLC: mobile phase 950:50:2 n-hexane:2-propanol:HOAc, flow rate 1.0 mL/min, 254 nm, chiralpak AD 4.6 x 250 mm, column temp 40°C, sample concentration approximately 0.5 mg/mL in 90:10 n-hexane:2-propanol, authentic racemate retention times 3.6 and 4.6 min. (-)-(2R, 4S)-4-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester mono ethanolate shows 4.6 min, 99.1% and 3.6 min, not detected; $[\alpha]_D$ = -93.3 (c = 1.08, CH_3OH).

Example 9

Anhydrous, (-)-(2R,4S)-4-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester.

A 2.6g portion of 4(S)-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2(R)-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (a mixture of predominantly amorphous material with traces of ethanolate crystalline form; the title compound was also prepared in an analogous manner starting from pure amorphous or pure ethanolate material) was charged to 13 milliliters of hexanes and heated to effect a solution at about 60°C. The heat was removed and the reaction was allowed to cool to ambient over a one hour period. The reaction was seeded with anhydrous (-)-(2R,4S)-4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester and granulated for eighteen hours under ambient conditions. Alternately, the anhydrous crystals may be prepared from hexanes without seeding. The product was collected by filtration and air dried. The isolated product X-ray pattern matched the calculated powder pattern.

Density: 1.406

Crystal System: Trigonal

Microscopy: Well formed rods and equant (fractured rods) crystals demonstrating high birefringence when viewed across the C axis. Being in the Trigonal crystal system the crystals do not demonstrate birefringence when viewed down the C axis. The crystals demonstrate a cleavage plane perpendicular to the C axis.

Fusion Microsocopy: In Type A oil--------dissolution at 50°C.

Dry----------clear melt at 86°C.

NMR: No trace of ethanolate

Degree of crystallinity: Highly crystalline

Hygroscopicity: Non-hygroscopic at 100% relative humidity over 48 hours.

Appearance: Free flowing white powder.

The X-Ray diffraction d-spacing is provided in Table 2.

TABLE 2

Anode: CU – Wavelength 1: 1.54056 Wavelength 2: 1.54439 (Rel Intensity: 0.500)
Range #1 – Coupled: 3.000 to 40.000 StepSize: 0.040 StepTime: 1.00
Smoothing Width: 0.300 Threshold: 1.0

d(A)	1(rel)	d(A)	I(rel)	d(A)	I(rel)
11.21659	34.8	5.52958	60.0	4.04469	36.6
10.50618	12.0	5.39152	75.7	3.89345	39.6
9.66890	11.0	5.24818	80.5	3.72038	80.7
8.88669	4.1	4.84992	13.2	3.64330	15.0
7.31083	3.7	4.44170	100.0	3.49463	5.9
6.34185	56.4	4.32558	16.8	3.44831	7.2
6.09484	5.9	4.25150	31.0	3.33631	14.7
5.92806	38.4	4.08413	42.7	3.22157	6.7

d(A)	I(rel)	d(A)	I(rel)
3.16983	8.3	2.57207	8.5
3.11970	14.0	2.49503	3.6
2.96985	16.3	2.44562	
2.87051	8.7	2.42250	
2.81002	6.8	2.38844	
2.75539	6.8	2.36135	
2.70226	3.6	2.32612	
2.64524	8.9		

Example 10

Monoethanolate, (-)-(2R,4S)-4-[(3,5-Bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester.

4.0 grams of (-)-(2R,4S)-4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester were dissolved in 3.5 ml ethanol and sonicated for two minutes to complete dissolution. A white solid formed to which 10 ml ethanol was added and stirred at ambient temperature overnight. A white powder was filtered and collected on 0.22 μm LS filter paper followed by washing with about 15 ml. ethanol. The isolated product X-ray pattern matched the calculated powder pattern.

Density: 1.402

Crystal System: orthorhombic

Microscopy: crystalline needles with moderate birefringence.

Fusion Microsocopy: In Type A oil-----melt and dissolution at 43°C with loss of water

Dry----------clear melt at 43°C

NMR: shows ethanol of solvation

Degree of crystallinity: highly crystalline

Hygroscopicity: non-hygroscopic

Appearance: free-flowing white power

The X-Ray diffraction d-spacing is provided in Table 3.

TABLE 3

Anode: CU – Wavelength 1: 1.54056 Wavelength 2: 1.54439 (Rel Intensity: 0.500)
Range #1 – Coupled: 3.000 to 40.000 StepSize: 0.040 StepTime: 1.00
Smoothing Width: 0.300 Threshold: 1.0

d(A)	1(rel)	d(A)	I(rel)	d(A)	I(rel)
22.15759	37.6	5.69284	6.9	4.18443	23.3
8.61222	15.1	5.45839	5.8	4.03073	30.9
8.15185	9.5	5.19975	19.0	3.96396	33.9
7.83462	47.0	4.90695	53.6	3.83314	35.0
7.47295	100.0	4.68527	42.1	3.77447	40.8
7.00403	9.6	4.80453	18.9	3.72125	33.1
6.46476	17.2	4.38780	16.3	3.62106	26.6
6.23035	14.8	4.30354	19.7	3.52462	17.1
5.90921	7.9				

d(A)	I(rel)	d(A)	I(rel)
3.44170	12.6	2.77147	5.0
3.35282	6.7	2.70399	7.5
3.25110	11.7	2.63859	4.6
3.12884	5.7	2.53872	6.4
3.03164	4.4	2.49493	5.3
2.94892	5.8	2.47186	5.0
2.86853	4.2	2.34837	4.7
2.79318	4.3	2.26951	4.1

Example 11

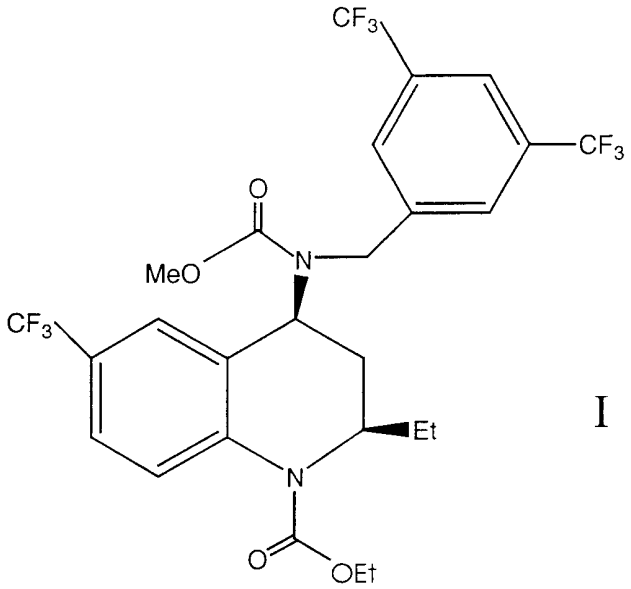
Anhydrous (-)-(2R,4S)-4-[(3,5-bis-trifluromethylbenzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester.

A crude solution of approximately 42 g of (-)-(2R,4S)-4-[(3,5-bis-trifluromethylbenzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester in 500 ml of ethyl acetate (obtained via the process described in Example 8) was concentrated under vacuum to a volume of 100-135 ml. The remaining ethyl acetate was displaced with 3 X 220 ml 2B EtOH to a final volume

of 100-135 ml. This solution was seeded with a crystal of anhydrous (-)-(2R,4S)-4-[(3,5-bis-triflurомethylbenzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester. After stirring 18 hr at room temperature the slurry was filtered and vacuum dried to give 19.81 g of anhydrous (-)-(2R,4S)-4-[(3,5-bis-triflurомethylbenzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester. The melting point behaviour was the same as the material prepared via Example 9 confirming the anhydrous nature of the material.

CLAIMS

1. A crystalline form of the compound of formula I



I

2. A crystal which is anhydrous [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester.

3. A crystal which is the ethanolate of [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester.

4. A crystal of claim 1 which is the anhydrous crystal having the x-ray powder diffraction d-spacing

Anode: CU – Wavelength 1: 1.54056 Wavelength 2: 1.54439 (Rel Intensity: 0.500)
Range #1 – Coupled: 3.000 to 40.000 StepSize: 0.040 StepTime: 1.00
Smoothing Width: 0.300 Threshold: 1.0

d(A)	1(rel)	d(A)	I(rel)	d(A)	I(rel)
11.21659	34.8	5.52958	60.0	4.04469	36.6
10.50618	12.0	5.39152	75.7	3.89345	39.6
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7.31083	3.7	4.44170	100.0	3.49463	5.9
6.34185	56.4	4.32558	16.8	3.44831	7.2
6.09484	5.9	4.25150	31.0	3.33631	14.7
5.92806	38.4	4.08413	42.7	3.22157	6.7

5

d(A)	I(rel)	d(A)	I(rel)
3.16983	8.3	2.57207	8.5
3.11970	14.0	2.49503	3.6
2.96985	16.3	2.44562	
2.87051	8.7	2.42250	
2.81002	6.8	2.38844	
2.75539	6.8	2.36135	
2.70226	3.6	2.32612	
2.64524	8.9		

5. A crystal of claim 1 which is the ethanolate crystal having the x-ray powder diffraction d-spacing

Anode: CU – Wavelength 1: 1.54056 Wavelength 2: 1.54439 (Rel Intensity: 0.500)
Range #1 – Coupled: 3.000 to 40.000 StepSize: 0.040 StepTime: 1.00
Smoothing Width: 0.300 Threshold: 1.0

d(A)	1(rel)	d(A)	I(rel)	d(A)	I(rel)
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8.61222	15.1	5.45839	5.8	4.03073	30.9
8.15185	9.5	5.19975	19.0	3.96396	33.9
7.83462	47.0	4.90695	53.6	3.83314	35.0
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7.00403	9.6	4.80453	18.9	3.72125	33.1
6.46476	17.2	4.38780	16.3	3.62106	26.6
6.23035	14.8	4.30354	19.7	3.52462	17.1
5.90921	7.9				

d(A)	I(rel)	d(A)	I(rel)
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3.25110	11.7	2.63859	4.6
3.12884	5.7	2.53872	6.4
3.03164	4.4	2.49493	5.3
2.94892	5.8	2.47186	5.0
2.86853	4.2	2.34837	4.7
2.79318	4.3	2.26951	4.1

6. A pharmaceutical composition which comprises a therapeutically effective amount of a crystal of claim 1 and a pharmaceutically acceptable carrier, vehicle or diluent.

7. The pharmaceutical composition as recited in claim 6 wherein the pharmaceutical composition comprises an atherosclerosis, peripheral vascular disease, dyslipidemia, hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial-hypercholesterolemia, cardiovascular disorders, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, reperfusion injury, angioplastic restenosis, hypertension, vascular

complications of diabetes, obesity or endotoxemia treating amount of the crystal of claim 1 and a pharmaceutically acceptable carrier, vehicle or diluent.

8. The pharmaceutical composition as recited in claim 6 for the treatment of atherosclerosis which comprises an atherosclerosis treating amount of a crystal of Formula I and a pharmaceutically acceptable carrier, vehicle or diluent.

9. The pharmaceutical composition as recited in claim 8 wherein the atherosclerosis treating amount of the Formula I crystal is about 0.1 to 10 mg/kg/day, and the pharmaceutical composition was prepared by dissolving the crystal of claim 1 in a fatty oil.

10. The pharmaceutical composition as recited in claim 8 wherein the Formula I crystal is anhydrous.

11. The pharmaceutical composition as recited in claim 8 wherein the Formula I crystal is the ethanolate crystal.

12. A method of inhibiting CETP in a mammal in need thereof which comprises the administration of a CETP inhibiting amount of the Formula I crystal as recited in claim 1.

13. The method as recited in claim 12 comprising treating atherosclerosis, peripheral vascular disease, dyslipidemia, hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial-hypercholesterolemia, cardiovascular disorders, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, reperfusion injury, angioplastic restenosis, hypertension, vascular complications of diabetes, obesity or endotoxemia by administering to a mammal, in need of such treatment a therapeutically effective amount of the Formula I crystal.

14. The method as recited in claim 13 wherein atherosclerosis is treated with an atherosclerosis treating amount of the Formula I crystal.

15. The method as recited in claim 14 wherein the atherosclerosis treating amount of the Formula I crystal is about 0.1 to 10 mg/kg/day and the Formula I crystal was dissolved in a fatty oil.

16. The method as recited in claim 15 wherein the Formula I crystal is anhydrous.

17. The method as recited in claim 15 wherein the Formula I salt is the ethanolate.

18. A process for preparing crystalline anhydrous [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-

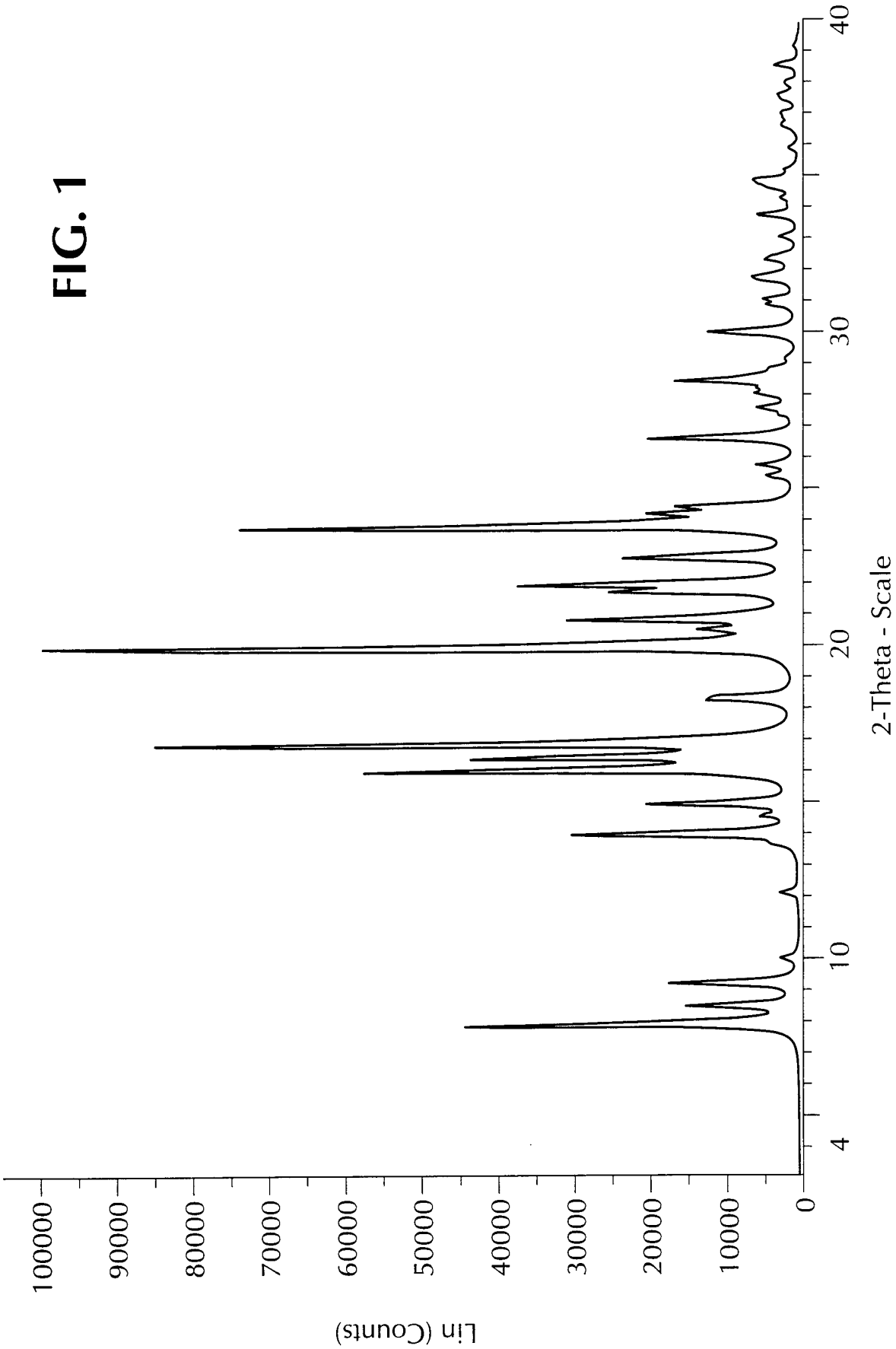
2H-quinoline-1-carboxylic acid ethyl ester comprising dissolving or mixing [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester in hexanes at ambient temperature for about 2 to about 24 hours wherein said precursor is not an anhydrous crystalline form.

19. A process for preparing crystalline ethanolate [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester by dissolving or mixing [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester in ethanol/water at ambient temperature for about 0.5 to about 18 hours wherein said precursor is not a crystalline ethanolate form.

20. The process as recited in claim 19 wherein ethanol is used without water.

21. A process for preparing crystalline anhydrous [2R,4S] 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester comprising dissolving or mixing [2R,4S] 4-[3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester in ethanol at ambient temperature for about 2 to about 24 hours wherein said precursor is not an anhydrous crystalline form.

FIG. 1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10
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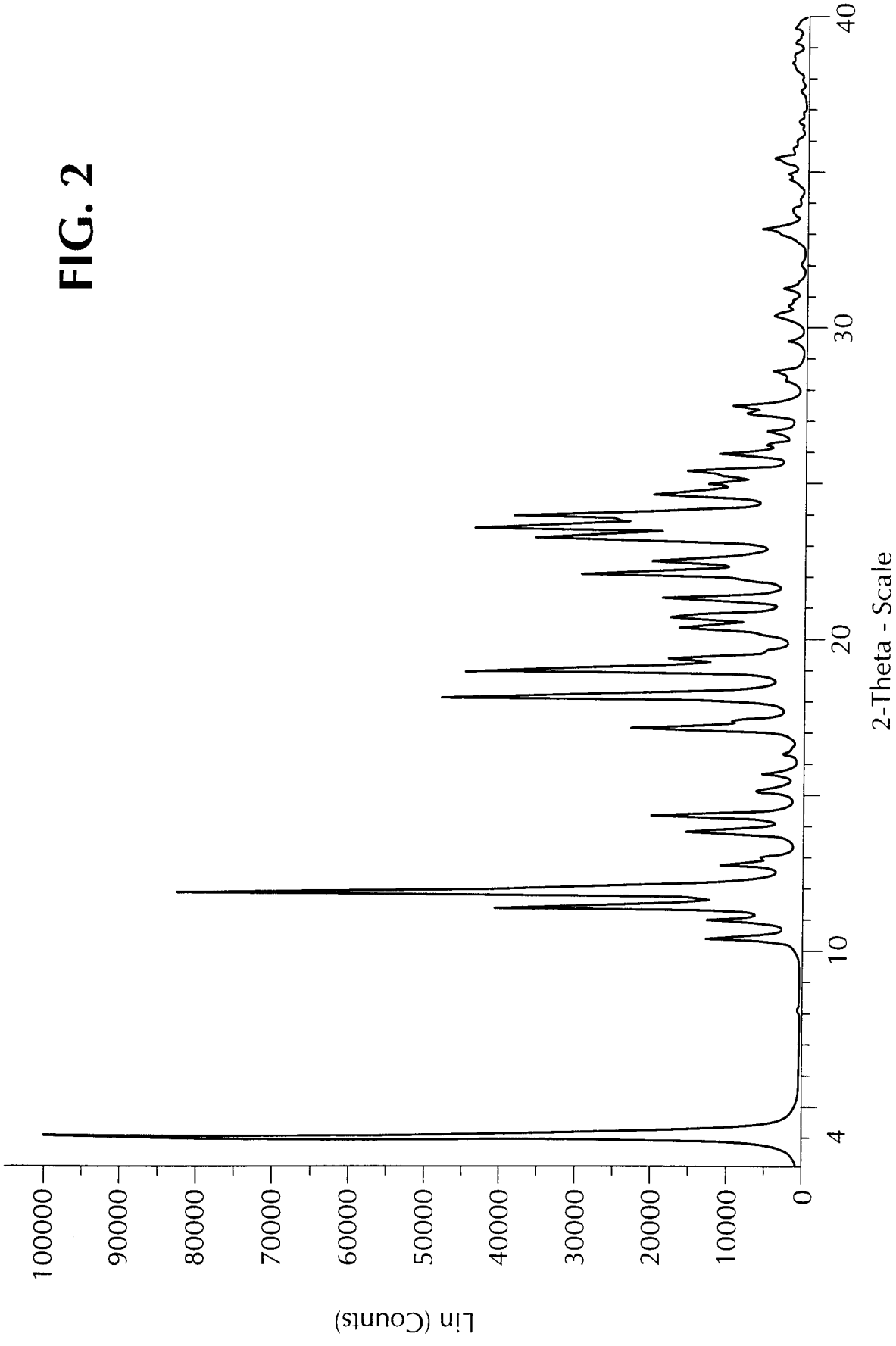
40
2-Theta - Scale

FIG. 2


Lin (Counts)
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
4
10
20
30
40
2-Theta - Scale

INTERNATIONAL SEARCH REPORT

Interr. nal Application No
PCT/IB 00/01650

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D215/42 A61K31/47 A61P9/10

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 7 C07D A61K A61P

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 00 17164 A (WESTER RONALD THURE ;PFIZER PROD INC (US); DENINNO MICHAEL PAUL (U) 30 March 2000 (2000-03-30) page 66, line 14-16; example 120	1-11, 18-21
A	WO 98 33775 A (AMERICAN HOME PROD) 6 August 1998 (1998-08-06) page 1; claim 1	1-11
A	US 5 231 102 A (BAKER RAYMOND ET AL) 27 July 1993 (1993-07-27) column 1-2	1-11

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

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

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

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

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 January 2001	23/01/01

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Lauro, P

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 00/01650

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 12 to 17 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interr nal Application No
PCT/IB 00/01650

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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