

[54] ERYTHRO-(E)-7-[3'-C₁₋₃ALKYL-1'-(3'',5''-DIMETHYLPHENYL)NAPHTH-2'-YL]-3,5-DIHYDROXYHEPT-6-ENOIC ACIDS AND DERIVATIVES THEREOF

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Related U.S. Application Data

[63] Continuation of Ser. No. 633,809, Jul. 24, 1984, abandoned.

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[52] U.S. Cl. 514/532; 560/56; 562/466; 549/292; 514/557; 514/824

[58] Field of Search 549/289, 274, 292, 291, 549/415, 417; 560/104, 56, 59, 119; 514/451, 532, 557; 562/501, 466

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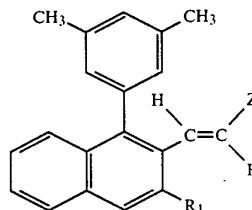
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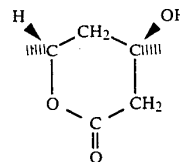
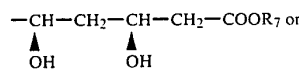
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[57] ABSTRACT

Compounds of the formula



wherein
 R₁ is C₁₋₃alkyl, and
 Z is



wherein R₇ is hydrogen, R₈ or M,
 wherein
 R₈ is a physiologically acceptable and hydrolyzable ester group, and
 M is a pharmaceutically acceptable cation,

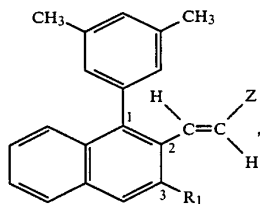
the use thereof for inhibiting cholesterol biosynthesis and lowering the blood cholesterol level and, therefore, in the treatment of hyperlipoproteinemia and atherosclerosis, pharmaceutical compositions comprising such compounds and processes for and intermediates in the synthesis of such compounds.

15 Claims, No Drawings

ERYTHRO-(E)-7-[3'-C₁₋₃ALKYL-1'-(3'',5''-DIMETHYLPHENYL)NAPHTH-2'-YL]-3,5-DIHYDROXYHEPT-6-ENOIC ACIDS AND DERIVATIVES THEREOF

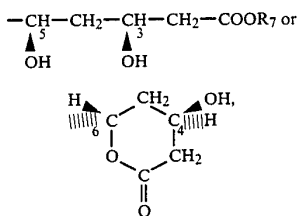
This application is a continuation of application Ser. No. 633,809, filed July 24, 1984 and now abandoned.

This invention relates to compounds of the formula



wherein

R₁ is C₁₋₃alkyl, and
Z is



wherein R₇ is hydrogen, R₈ or M,

wherein

R₈ is a physiologically acceptable and hydrolyzable ester group, and

M is a pharmaceutically acceptable cation, processes for and intermediates in the synthesis thereof, pharmaceutical compositions comprising a compound of Formula I and the use of the compounds of Formula I for inhibiting cholesterol biosynthesis and lowering the blood cholesterol level and, therefore, in the treatment of hyperlipoproteinemia and atherosclerosis.

By the term "physiologically acceptable and hydrolyzable ester group" is meant a group which, together with the —COO— radical to which it is attached, forms an ester group which is physiologically acceptable and hydrolyzable under physiological conditions to yield a compound of Formula I wherein R₇ is hydrogen and an alcohol which itself is physiologically acceptable, i.e., non-toxic at the desired dosage level, and which, preferably, is free of centers of asymmetry. Examples of such groups are C₁₋₃alkyl, n-butyl, i-butyl, t-butyl and benzyl, collectively referred to as R₈'.

As is self-evident to those in the art, each compound of Formula I (and every subscope and species thereof) has two centers of asymmetry (the two carbon atoms bearing the hydroxy groups in the group of Formula a and the carbon atom bearing the hydroxy group and the carbon atom having the free valence in the group of Formula b) and, therefore, there are two stereoisomeric forms (enantiomers) of each compound (a racemate), provided that R₇ does not contain any center of asymmetry. The two stereoisomers of the compounds wherein Z is a group of Formula a are the 3R,5S and 3S,5R isomers and the two stereoisomers of the com-

pounds wherein Z is a group of Formula b are the 4R,6S and 4S,6R isomers, both the individual stereoisomers and the racemates being within the scope of this invention. When R₇ contains one or more centers of asymmetry, there are four or more stereoisomers. Since it is preferred that R₇ not contain a center of asymmetry and for reasons of simplicity any additional stereoisomers resulting from the presence of one or more centers of asymmetry in R₇ will be ignored, it being assumed that R₇ is free of centers of asymmetry.

(i) The preferred stereoisomer of each compound wherein Z is a group of Formula a is the 3R,5S isomer and the preferred stereoisomer of each compound wherein Z is a group of Formula b is the 4R,6S isomer. These preferences also apply to the compounds of Formula I having more than two centers of asymmetry and represent the preferred configurations of the indicated positions.

R₁ is preferably methyl or isopropyl.

R₇ is preferably R₇', where R₇' is hydrogen, C₁₋₃alkyl or M, more preferably R₇'', where R₇'' is hydrogen, C₁₋₃alkyl or M, and most preferably M, especially sodium. M is preferably M' and most preferably sodium.

(a) R₈ is preferably R₈', where R₈' is C₁₋₃alkyl, n-butyl, i-butyl, t-butyl or benzyl, more preferably C₁₋₃alkyl and most preferably C₁₋₂alkyl.

M is preferably free from centers of asymmetry and is more preferably M', i.e., sodium, potassium or ammonium, and most preferably sodium. For simplicity, each of the formulae in which M appears (in the specification and the claims) has been written as if M were monovalent and, preferably, it is. However, it may also be divalent or trivalent and, when it is, it balances the charge of two or three carboxy groups, respectively.

The preferred compounds of Formula I wherein Z is a group of Formula a are those

- (i) wherein R₇ is R₇',
- (ii) of (i) wherein R₇ is R₇'',
- (iii) of (ii) wherein R₇ is M,
- (iv) of (iii) wherein R₇ is M',
- (v) of (iv) wherein R₇ is sodium, and
- (vi)-(x) of (i)-(v) wherein R₁ is methyl or isopropyl.

Groups (i)-(x) embrace the 3R,5S-3S,5R racemates and the 3R,5S and 3S,5R enantiomers, of which the racemates and the 3R,5S enantiomers are preferred.

The preferred compounds of Formula I wherein Z is a group of Formula b are those wherein R₁ is methyl or isopropyl. This group embraces the 4R,6S-4S,6R racemates and the R,6S and 4S,6R enantiomers, of which the racemates and the R,6S enantiomers are preferred.

The compounds of Formula I wherein R₁ is methyl, and Z is a group of Formula a wherein R₇ is hydrogen, ethyl or a group of Formula b are synthesized as set forth in Examples 1-5.

The compounds of Formula I wherein R₁ is ethyl, and Z is a group of Formula a wherein R₇ is hydrogen, ethyl or sodium or a group of Formula b may be synthesized by the processes of Examples 1-5 with the following additional step: The compound of Formula CCXLII is converted to the corresponding compound having an ethyl group in the 3-position of the naphthalene ring by the procedure utilized to convert the compound of Formula CCXLI to the compound of Formula CCXLII, i.e., the procedure of Step 8 of Example 1. Otherwise, the synthesis is the same.

The compounds of Formula I wherein R₁ is isopropyl, and Z is a group of Formula a wherein R₇ is hydro-

gen, ethyl or sodium or a group of Formula b may be synthesized by the processes of Example A, Steps 9-13 of Example 1 and Examples 2-5. The corresponding compounds of Formula I wherein R₁ is n-C₁₋₃alkyl may be synthesized analogously utilizing in Step 8 of Example A the corresponding n-C₁₋₃alkylmagnesium chloride or bromide in lieu of isopropylmagnesium chloride.

The compounds of Formula I wherein Z is a group of Formula a wherein R₇ is any other significance of R₈' may be synthesized by the processes of the preceding three paragraphs utilizing appropriate starting materials.

The compounds of Formula I wherein Z is a group of Formula a wherein R₇ is R₈ may be synthesized by reacting the corresponding compound wherein Z is a group of Formula b with at least 2, e.g., 2-10, preferably 2.05-2.5, moles of a compound of the formula M₂⊕⊖OR₈, wherein M₂ is sodium or potassium, per mole of the compound wherein Z is a group of Formula b, at 0°-70° C., preferably 20°-50° C., for 2-12 hours, in an inert organic solvent, preferably an inert ether solvent such as tetrahydrofuran or, if the corresponding alcohol of the formula R₈-OH is a liquid at the desired reaction temperature, preferably said corresponding alcohol. By the term "corresponding alcohol" is meant that R₈ in the compound of the formula M₂⊕⊖OR₈ and in the alcohol of the formula R₈-OH is the same. The compounds of Formula I wherein Z is a group of Formula a wherein R₇ is R₈ may also be prepared by esterifying the corresponding compound wherein R₇ is hydrogen with an alcohol of the formula R₈-OH. Conveniently, the compound wherein R₇ is hydrogen is treated with a large excess of the alcohol of the formula R₈-OH (e.g., 2-50 moles per mole of the compound wherein R₇ is hydrogen) at 20°-40° C. for 2-12 hours in the presence of a catalytic amount of an acid such as p-toluenesulfonic acid. The excess alcohol serves as the solvent. The reaction may also be run in an inert organic solvent, e.g., an ether such as tetrahydrofuran, and must be run in such a solvent if the alcohol of the formula R₈-OH is not a liquid at the desired reaction temperature.

The compounds of Formula I wherein Z is a group of Formula a wherein R₇ is M may be synthesized by neutralizing the corresponding compounds wherein R₇ is hydrogen with 0.95-1, preferably 0.96-0.99, equivalent of a base of the formula M⊕⊖OH per mole of the compound wherein R₇ is hydrogen at 0°-25° C., preferably 20°-25° C., for 1-10 minutes, in an inert aqueous organic solvent, for example a mixture of water and a C₁₋₂alkanol. As should be evident from what is set forth above, the formula M⊕⊖OH embraces bases of the formulae M⊕²(⊖OH)₂ and M⊕³(⊖OH)₃.

The processes described above yield racemates. However, techniques for separating a racemate into its two optically active enantiomers are known. For example, a racemic compound having a carboxylic acid group may be reacted with an optically pure organic base having at least one center of asymmetry to form a mixture of diastereoisomeric salts or amides that may be separated by fractional crystallization, column chromatography, preparative thin layer chromatography, high pressure liquid chromatography, etc. or it may be reacted with an optically pure alcohol having at least one center of asymmetry to form a mixture of diastereoisomeric esters which may be separated by conventional techniques such as those set forth above. On the other hand, a racemic compound having a hydroxy group, for

example a compound of Formula I wherein Z is a group of Formula b, may be esterified with an optically pure carboxylic acid having at least one center of asymmetry to form a mixture of diastereoisomeric esters or it may be reacted with an optically pure trisubstituted silyl halide having an asymmetric silicon atom, for example (-)-α-naphthylphenylmethylchlorosilane (Sommer et al., J. Am. Chem. Soc. 80, 3271 (1958).), to form a mixture of two diastereoisomeric silyloxy compounds, which mixture may be separated by conventional techniques. After separation, the optically pure salts, amides, esters or silyloxy compounds are reconverted to the corresponding carboxy group- or hydroxy group-containing compounds with retention of optical purity. For example, (-)-α-naphthylphenylmethylsilyl and other silyl groups may be cleaved with a fluoride reagent, for example, tetra-n-butylammonium fluoride in an anhydrous inert organic medium containing glacial acetic acid, preferably tetrahydrofuran containing 1-2 moles, preferably 1.2-1.5 moles, of glacial acetic acid per mole of the fluoride compound. The reaction temperature is suitably 20°-60° C., preferably 20°-30° C., and the reaction time is suitably 8-24 hours, particularly when the reaction temperature is 20°-30° C. Approximately 1-5 moles, preferably 2-4 moles, of fluoride reagent per mole of the silyl group-containing compound are utilized. The reaction mixture should be acidic at the time the fluoride reagent is added to maximize production of the desired product.

Most of the processes described above are described in greater detail in my application Ser. No. 06/570,584, filed Jan. 13, 1984 and now abandoned and titled Naphthalene And Tetrahydronaphthalene Derivatives Of Mevalonolactone and Derivatives Thereof. Where the reaction conditions set forth in said application differ from those set forth herein, the reaction conditions set forth in said application may also be utilized for the compounds of this specification. Said application, particularly pages 15-67, 109-118 and 125-151, is hereby incorporated by reference.

Also described in said application Ser. No. 06/570,584 are processes by which the 4R,6S isomers of the compounds of Formula I wherein Z is a group of Formula b and the 3R,5S isomers of the compounds of Formula I wherein Z is a group of Formula a may be synthesized.

All of the reagents and reactants the synthesis of which is not described in this specification are either known or are synthesizable by processes analogous to those described in the literature for similar known compounds.

The product of each reaction may, if desired, be purified by conventional techniques such as recrystallization (if a solid), column chromatography, preparative thin layer chromatography, gas chromatography (if sufficiently volatile), fractional distillation under high vacuum (if sufficiently volatile) or high pressure liquid chromatography. Often, however, the crude product of one reaction may be employed in the following reaction without purification.

Since any compound of Formula I wherein Z is a group of Formula a wherein R₇ is a cation other than M may be converted into the corresponding compounds wherein R₇ is hydrogen, M or R₈ by acidification optionally followed by neutralization or esterification, ion exchange, etc., the compounds of Formula I wherein Z is a group of Formula a and R₇ is a pharmaceutically unacceptable cation are also within the scope of this

invention inasmuch as they are useful as intermediates. However, such compounds are not compounds of Formula I as utilized in this specification, except where indicated to the contrary.

Besides having the utility set forth below, every compound of Formula I is useful as an intermediate in the synthesis of one or more other compounds of Formula I utilizing the reactions set forth in this specification, e.g., those of Examples 2-5.

Also within the scope of this invention are the intermediates of Formulae CCXLI-CCXLVI and the compounds corresponding to those of Formulae CCXLII-CCXLVI but having a C₂₋₃alkyl group in the 3-position of the naphthalene ring in lieu of the methyl group and those corresponding to that of Formula CCXLVI but having, in lieu, of the ethyl group, a different significance of R₈' and, optionally, in lieu of the methyl group in the 3-position of the naphthalene ring, a C₂₋₃alkyl group.

The compounds of Formula I are competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate limiting enzyme in cholesterol biosynthesis, and, therefore, they are inhibitors of cholesterol biosynthesis. Consequently, they are useful for lowering the blood cholesterol level in animals, e.g., mammals, especially larger primates, and, therefore, as hypolipoproteinemic and antiatherosclerotic agents. The biological activity of the compounds of Formula I may be demonstrated in the following three tests:

Test A. In Vitro Microsomal Assay of HMG-CoA Reductase Inhibition:

200 μ l. aliquots (1.08-1.50 mg./ml.) of rat liver microsomal suspensions, freshly prepared from male Sprague-Dawley rats (150-225 g. body weight), in Buffer A with 10 mmol. dithiothreitol are incubated with 10 μ l. of a solution of the test substance in dimethylacetamide and assayed for HMG-CoA reductase activity as described in Ackerman et al., *J. Lipid Res.* 18, 408-413 (1977). In the assay the microsomes are the source of the HMG-CoA reductase enzyme which catalyzes the reduction of HMG-CoA to mevalonate. The assay employs a chloroform extraction to separate the product, [¹⁴C]mevalonolactone, formed by the HMG-CoA reductase reaction from the substrate, [¹⁴C]HMG-CoA. [³H]mevalonolactone is added as an internal reference. Inhibition of HMG-CoA reductase is calculated from the decrease in specific activity ([¹⁴C/³H]mevalonate) of test groups compared to controls.

Test B. In Vitro Cell Culture Cholesterol Biosynthesis Screen:

The cell culture is prepared as follows: Stock monolayer cultures of the Fu5AH rat hepatoma cell line (originally obtained from G. Rothblat; see Rothblat, *Lipids* 9, 526-535 (1974)) are routinely maintained in Eagle's Minimum Essential Medium (EMEM) supplemented with 10% fetal bovine serum (FBS) in 75 cm.² tissue culture flasks. For these studies, when the cultures reach confluence, they are removed by mild enzymatic treatment with 0.25% trypsin in Hanks' balanced salt solution (without calcium and magnesium). After centrifugation of the cell suspension and aspiration of the enzymatic solution, the cell pellet is resuspended in an appropriate volume of media for seeding into 60 mm. tissue culture dishes. The cultures are incubated at 37° C. in an atmosphere of high humidity and 5% carbon dioxide. When the cultures are confluent (approximately 5 days), they are ready for use. The culture

media is aspirated from the dishes and replaced with 3 ml. of EMEM supplemented with 5 mg./ml. of delipidized serum protein (DLSP) prepared by the method of Rothblat et al., *In Vitro* 12, 554-557 (1976). Replacement of the FBS with DLSP has been shown to stimulate the incorporation of [¹⁴C]acetate into sterol by removing the exogenous sterol supplied by the FBS, thereby requiring the cells to synthesize sterol. Enhanced 3-hydroxy-3-methylglutaryl Coenzyme A reductase (HMG-CoA reductase) activity is measurable in the cells in response to the lack of exogenous sterol. Following approximately 24 hours incubation at 37° C. in the DLSP supplemented media, the assay is initiated by the addition of 3 μ Ci of [¹⁴C]acetate and the test substance solubilized in dimethylsulfoxide (DMSO) or distilled water. Solvent controls and compactin-treated controls are always prepared. Triplicate 60 mm. tissue culture dishes are run for each group. After 3 hours incubation at 37° C., the cultures are examined microscopically using an inverted phase contrast microscope. Notations are made of any morphological changes which may have occurred in the cultures. The media is aspirated and the cell layer is gently washed twice with 0.9% sodium chloride solution (saline). The cell layer is then harvested in 3 ml. of 0.9% saline by gentle scraping with a rubber policeman and transferred to a clean glass tube with Teflon lined cap. The dishes are rinsed with 3 ml. of 0.9% saline and rescraped, and the cells are combined with the first harvest. The tubes are centrifuged at 1500 r.p.m. for 10 minutes in an IEC PR-J centrifuge, and the supernatant is aspirated.

The cells are then extracted as follows: One ml. of 100% ethanol is added to the cell pellet followed by sonication for 10 seconds with a "LO" setting of 50 on a Bronwell Biosonik IV. One hundred μ l. are taken for protein determination. One ml. of 15% potassium hydroxide (KOH) is added, and the samples are thoroughly vortexed. Saponification is accomplished by heating the ethanol-KOH treated samples at 60° C., for 60 minutes in a water bath. Following dilution of the samples with 2 ml. of distilled water, they are extracted three times with 7 ml. of petroleum ether. The petroleum ether extracts are then washed three times with 2 ml. of distilled water and finally taken to dryness under a stream of nitrogen.

The obtained samples are then analyzed by thin layer chromatography (TLC) as follows: Residues from the petroleum ether extraction are taken up in a small volume of hexane and spotted on silica gel 60 TLC plates (E. Merck). Development of the plates is carried out in a three phase solvent system consisting of 150 parts by volume hexane: 50 parts by volume diethyl ether: 5 parts by volume glacial acetic acid. Visualization is accomplished in an iodine vapor chamber. The plates are divided into five sections such that each section contains the molecules having the following approximate R_f values: section 1—0-0.4, section 2—0.4-0.55, section 3—0.55-0.7, section 4—0.7-0.9 and section 5—0.9-1.0. Section 2 contains the non-saponifiable sterols. The five sections of the TLC plates are scraped into scintillation vials. Blanks are also prepared from scrapings of chromatographed non-labelled standards. ACS® scintillation cocktail is added, and the radioactivity is determined in a liquid scintillation spectrometer. [¹⁴C]hexadecane standards are used to determine counting efficiencies. The total protein content of the samples is determined employing the Bio-Rad Protein Assay System.

The results are reported as disintegrations per minute per mg. protein (d.p.m./mg. protein) for each of the five TLC sections. Mean d.p.m./mg. protein \pm standard error of the mean are calculated, and drug treated means are compared for percentage change (% Δ) and statistical significance with solvent control means. TLC section 2 data is taken as a measure of HMG-CoA reductase activity inhibition.

Test C: In Vivo Cholesterol Biosynthesis Inhibition Test: In vivo studies utilize male Wistar Royal Hart rats weighing 150 ± 20 g. which have been kept for 7-10 days on an altered light cycle (6:30 A.M.-6:30 P.M. dark) housed two per cage and fed powdered Purina Rat Chow and water ad libitum. Three hours before the diurnal maximum of cholesterol synthesis at mid-dark, the rats are administered the test substance dissolved or as a suspension in 0.5% carboxymethylcellulose in a volume of 1 ml./100 g. body weight. Controls receive vehicle alone. One hour after receiving the test substance, the rats are injected intraperitoneally with about 25 μ Ci/100 g. body weight of sodium [14 C]acetate 1-3 mCi/mmol. Two hours after mid-dark, blood samples are obtained under sodium hexobarbital anesthesia and the serum is separated by centrifugation.

Serum samples are saponified and neutralized, and the 3β -hydroxysterols are precipitated with digitonin basically as described in Sperry et al., J. Biol. Chem. 187, 97 (1950). The [14 C]digitonides are then counted by liquid scintillation spectrometry. After correcting for efficiencies, the results are calculated in nCi (nanocuries) of sterol formed per 100 ml. of serum. Inhibition of sterol synthesis is calculated from the reduction in the nCi of sterols formed from test groups compared to controls.

The following results were obtained:

Test A:	Example 1	IC ₅₀ = 0.08 μ molar
	Example 2	IC ₅₀ = 0.01 μ molar
	Example 4	IC ₅₀ = 0.33 μ molar
	Compactin	IC ₅₀ = 0.77 μ molar
	Mevinolin	IC ₅₀ = 0.14 μ molar
IC ₅₀ is the concentration of the test substance in the assay system calculated to produce a 50% inhibition of HMG-CoA reductase activity.		
Test C:	Example 1	-35% at 0.5 mg./kg.
	Example 2	ED ₅₀ = 0.3 mg./kg.
	Example 4	-20% at 0.5 mg./kg.
	Compactin	ED ₅₀ = 3.5 mg./kg.
	Mevinolin	ED ₅₀ = 0.41 mg./kg.

As set forth above, the compounds of Formula I (including each and every subgroup thereof set forth in the specification and/or the claims) inhibit cholesterol biosynthesis and are useful for lowering the blood cholesterol level in animals, particularly mammals and more particularly larger primates, and, therefore, as hypolipoproteinemic and antiatherosclerotic agents.

The compounds of Formula I may be formulated into conventional pharmaceutical compositions and administered by conventional modes of administration. The compounds of each and every subgroup thereof in the specification and/or claims may likewise be formulated into conventional pharmaceutical compositions.

The compounds of Formula I may be combined with one or more pharmaceutically acceptable carriers and, optionally, one or more other conventional pharmaceutical adjuvants and administered orally in the form of tablets, dispersible powders, granules, capsules, elixirs, suspensions and the like or parenterally in the form of sterile injectable solutions or suspensions. The composi-

tions may be prepared by conventional means. The preferred pharmaceutical compositions from the standpoint of ease of preparation and administration are solid compositions, particularly tablets and capsules.

The precise dosage of the compound of Formula I to be employed for inhibiting cholesterol biosynthesis depends upon several factors including the host, the nature and the severity of the condition being treated, the mode of administration and the particular compound employed. However, in general, satisfactory inhibition or reduction of cholesterol biosynthesis (i.e., satisfactory reduction of the blood cholesterol level and satisfactory treatment of hyperlipoproteinemia and atherosclerosis) is achieved when a compound of Formula I is administered orally at a daily dosage of 0.01-100 mg./kg. body weight, e.g., 0.01-20 mg./kg. body weight for the compound of Example 2, or, for most larger primates, a daily dosage of 1-1000 mg. and suitably 1-150 mg., e.g., 5-100 mg., for the compound of Example 2.

The daily dosage is usually divided into two to four equal portions or administered in sustained release form. Usually, a small dosage is administered initially, and the dosage is gradually increased until the optimal dosage for the host under treatment is determined. For administration by injection, a dosage somewhat lower than would be used for oral administration of the same compound to the same host having the same condition is usually employed. However, the above dosages are also typically used for i.v. administration.

A typical dosage unit for oral administration may contain 0.5-500 mg. of a compound of Formula I. Preferred dosage units contain 0.5 to 75 mg. of a compound of Formula I, for example, 1-50 mg. of the compound of Example 2.

The compounds of Formula I (including those of each and every subgroup thereof) may be formulated into such pharmaceutical compositions containing an amount of the active substance that is effective for inhibiting cholesterol biosynthesis, such compositions in unit dosage form and such compositions comprising a solid pharmaceutically acceptable carrier.

A representative formulation prepared by conventional techniques for encapsulation in a hard gelatin capsule is:

Compound of Formula I, e.g., the compound of Example 2	25 mg.
Corn starch	224 mg.
Magnesium stearate	1 mg.

A representative formulation suitable for preparing tablets by conventional means is:

Compound of Formula I, e.g., the compound of Example 2	10 mg.
Polyvinylpyrrolidone USP	5 mg.
Powdered lactose	124 mg.
Corn starch	10 mg.
Magnesium stearate	1 mg.

The following examples show representative compounds encompassed by this invention and their synthesis. However, it should be understood that they are for purposes of illustration only.

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