United States Patent [19]

Terahara et al.

[11] **4,346,227**

[45] **Aug. 24, 1982**

[54] **ML-236B DERIVATIVES AND THEIR PREPARATION**

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[73] Assignee: **Sankyo Company, Limited,** Tokyo, Japan

[21] Appl. No.: **270,846**

[22] Filed: **Jun. 5, 1981**

[30] **Foreign Application Priority Data**

Jun. 6, 1980 [JP] Japan 55-76127
Aug. 22, 1980 [JP] Japan 55-115483
Sep. 8, 1980 [JP] Japan 55-124385
Sep. 19, 1980 [JP] Japan 55-130311

[51] **Int. Cl.**[3] **C07C 69/013**
[52] **U.S. Cl.** **560/119;** 560/256; 424/305; 435/135; 549/292
[58] **Field of Search** 560/119, 256

[56] **References Cited**

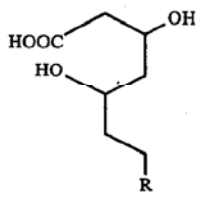
U.S. PATENT DOCUMENTS

4,137,322 1/1979 Endo et al. 424/273

Primary Examiner—Robert Gerstl
Attorney, Agent, or Firm—Frishauf, Holtz, Goodman & Woodward

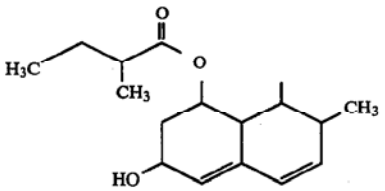
[57] **ABSTRACT**

Compounds of formula (I):

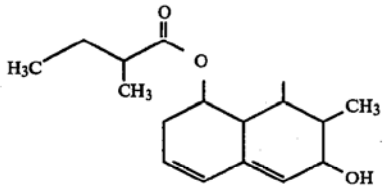


(I)

(wherein R represents a group of formula



or



and the corresponding ring-closed lactones, salts (especially alkali metal salts) and esters (especially C_1–C_5 alkyl esters) thereof may be prepared by subjecting ML-236B, or ML-236B carboxylic acid or a salt or ester thereof to enzymatic hydroxylation, which may be effected by means of microorganisms of the genera Mucor, Rhizopus, Zygorynchus, Circinella, Actinomucor, Gongronella, Phycomyces, Martierella, Pycnoporus, Rhizoctonia, Absidia, Cunninghamella, Syncephalastrum and Streptomyces, or cell-free, enzyme-containing extracts from said microorganisms. The compounds are capable of inhibiting biosynthesis of cholesterol and are thus useful in the treatment of hypercholesteraemia.

25 Claims, 5 Drawing Figures

Fig 1

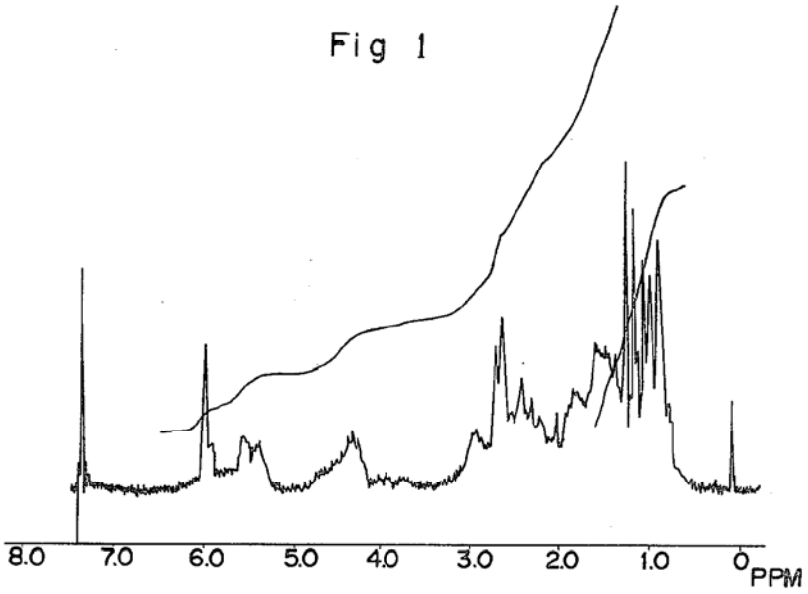


Fig 2

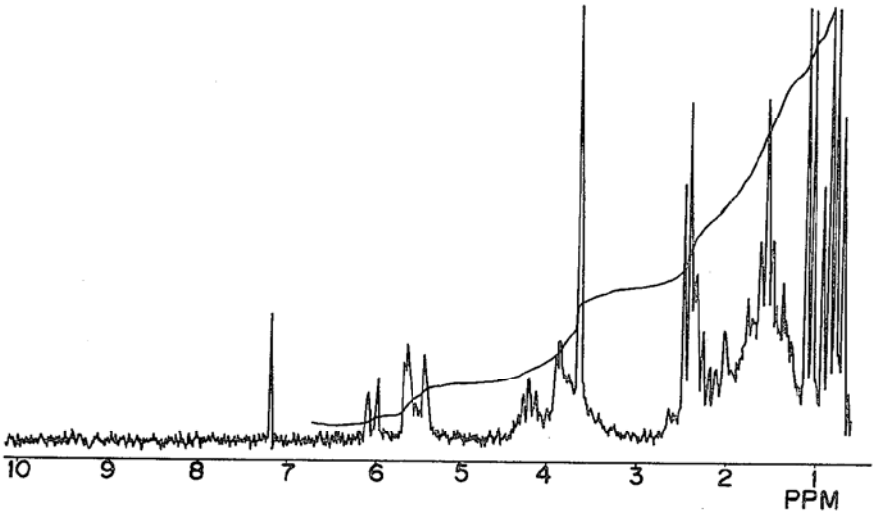


Fig 3

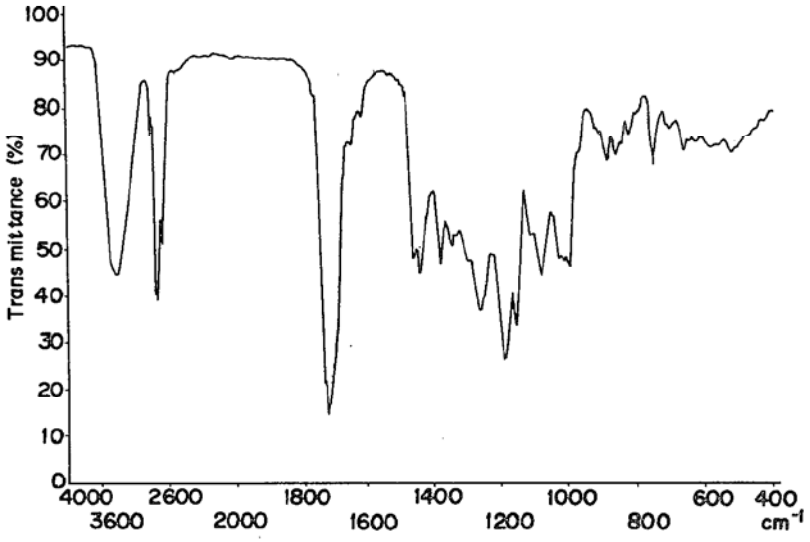


Fig 4

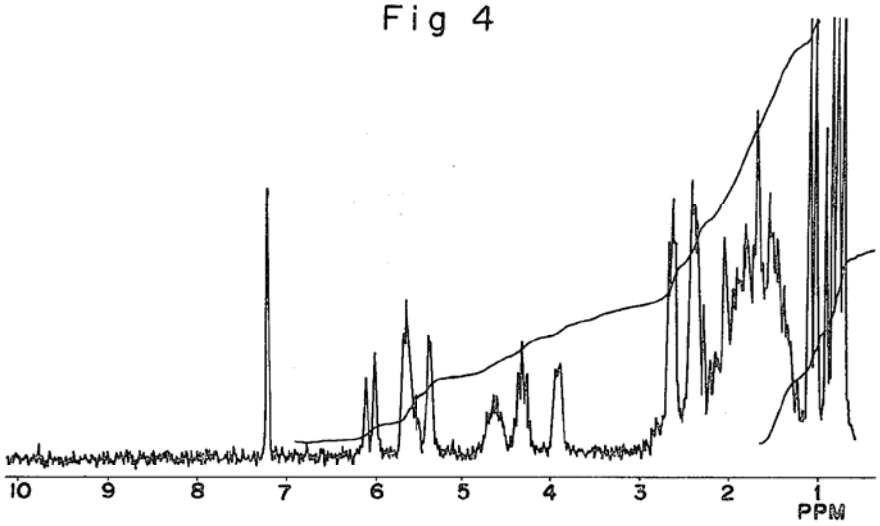
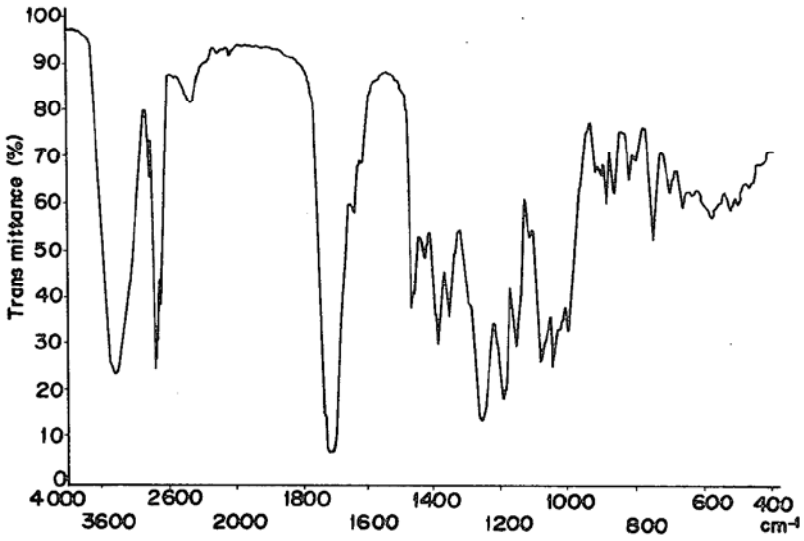


Fig 5

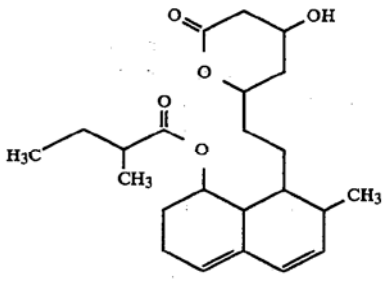


ML-236B DERIVATIVES AND THEIR PREPARATION

BACKGROUND OF THE INVENTION

The present invention relates to a series of new derivatives of the known compound ML-236B, to processes for their preparation and to pharmaceutical compositions containing them.

ML-236B, which has the following chemical structure:

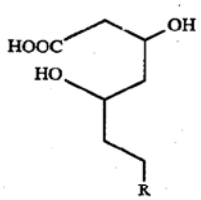


is disclosed in U.S. Pat. No. 3,983,140. It has been isolated and purified from the metabolic products of microorganisms of the genus Penicillium, especially *Penicillium citrinum*, a species of blue mould. It has been shown to inhibit the biosynthesis of cholesterol by enzymes or cultured cells separated from experimental animals by competing with the rate-limiting enzyme active in the biosynthesis of cholesterol, namely 3-hydroxy-3-methylglutaryl-coenzyme A reductase and, as a result, significantly reduces serum cholesterol levels of animals [Journal of Antibiotics, 29, 1346 (1976)]. A number of compounds structurally related to ML-236B have also been discovered and found to possess the ability to inhibit the biosynthesis of cholesterol.

We have now discovered a series of new compounds, which may be prepared by the enzymatic hydroxylation of ML-236B or of derivatives thereof, and which possess an ability to inhibit the biosynthesis of cholesterol which is at least comparable with, and in some instances substantially exceeds, that of ML-236B itself.

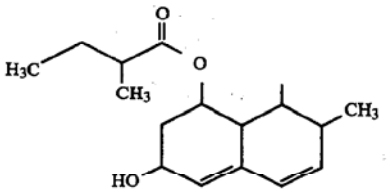
BRIEF SUMMARY OF INVENTION

The compounds of the present invention are those hydroxycarboxylic acids of formula (I):

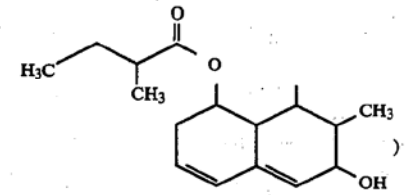


(I)

(in which R represents a group of formula



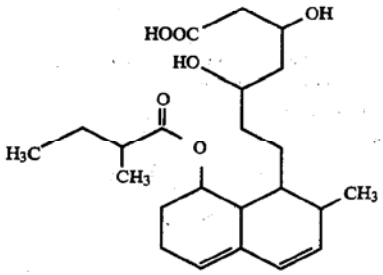
or



and ring-closed lactones, salts and esters thereof.

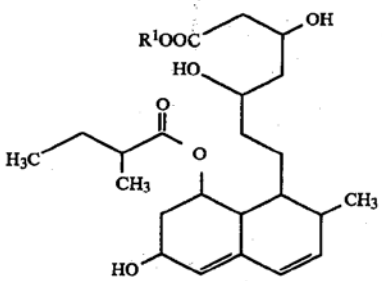
The invention also provides a process for preparing a compound of formula (I), or a ring-closed lactone, salt or ester thereof by the enzymatic hydroxylation of ML-236B, or ML-236B carboxylic acid, or a salt or ester thereof.

ML-236B carboxylic acid has the formula



DETAILED DESCRIPTION OF INVENTION

One class of compounds of the present invention are those compounds of formula (II):



(II)

(in which R^1 represents a hydrogen atom or a C_1–C_5 alkyl group), pharmaceutically acceptable salts of the acid wherein R^1 represents a hydrogen atom, and the corresponding lactone of formula (III):

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