HMG-CoA Reductase Inhibitors: An Exciting Development in the Treatment of Hyperlipoproteinemia

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I. INTRODUCTION

Coronary heart disease (CHD) continues to be one of the major health problems in all the developed countries of the world. A considerable body of clinical and epidemiological data has emerged over the years linking elevated blood levels of total cholesterol, Low Density Lipoprotein Cholesterol (LDL-C), and Very Low Density Lipoprotein Cholesterol (VLDL-C) as important risk factors for the development of coronary heart disease.[1]

For the treatment of elevated LDL-C and VLDL-C, a judicious diet, low in cholesterol and fat with saturated fatty acids replaced by polyunsaturated fatty acids, is the recommended choice. However, for patients nonresponsive

Medicinal Research Reviews, Vol. 11, No. 2, 121–146 (1991)

CCC 0198-6325/91/020121-26$04.00

to dietary intervention, the development of effective and safe therapeutic agents for the treatment of hyperlipoproteinemia remains an important need. This need has gained considerable support as a result of two important events: (1) the results of the Lipid Research Clinic's Coronary Primary Prevention Trial (LRC-CPPT), a multicenter, randomized, double-blind study involving 3806 asymptomatic middle-aged men in the United States with type II hyperlipoproteinemia, that demonstrated that a statistically significant reduction of 19% in the rate of fatal plus nonfatal coronary heart disease was associated with a 9% decrease in blood cholesterol levels,[2] and (2) the recommendation to treat individuals with blood cholesterol above the 75th percentile, which emerged from the consensus panel of the December, 1984 NIH Consensus Development Conference on the lowering of blood cholesterol to prevent coronary heart disease.[3]

In recent years, to achieve this goal of finding effective and safe therapeutic agents to lower LDL-cholesterol, great interest has focused on potent inhibitors of the enzyme β-Hydroxy-β-Methyl-Glutaryl-CoA reductase (HMG-CoA reductase, EC 1.1.1.34), which controls a key step in the endogenous synthesis of cholesterol. Several studies, both in animals and humans, have been reported with HMG-CoA reductase inhibitors: compactin (Mevastatin), CS-514 (Pravastatin, Mevalotin®, Pravachol®), mevinolin (Lovastatin, Mevacor®) and Synvinolin (Simvastatin, Zocor®),[4] which are structurally very closely related to one another. In order to assess fully the potential of HMG-CoA reductase inhibitors as an effective therapeutic intervention for the treatment of hyperlipoproteinemia, it is thus desirable to study in humans a variety of these inhibitors derived from different structural prototypes which can be distinguished in their overall biological profile from one another. This conceptual framework formed the basis for initiating efforts at the Sandoz Research Institute to develop and study a variety of HMG-CoA reductase inhibitors with chemical structures different in several respects from compactin, pravastatin (a hydroxy analog of compactin), lovastatin (a methyl analog of compactin), and simvastatin (a dimethyl analog of compactin), and has led to fluvastatin (XU 62-320), the first totally synthetic HMG-CoA reductase inhibitor currently in Phase III human clinical trials (Fig. 1).

II. DESIGN ASPECT FOR HMG-CoA REDUCTASE INHIBITORS AT SANDOZ RESEARCH INSTITUTE LEADING TO FLUVASTATIN (XU 62-320)

Investigations by Akira Endo with compactin[4] have to be largely credited for the resurgence of the research on cholesterol biosynthesis and the renewed interest in HMG-CoA reductase inhibitors, a field now almost three decades

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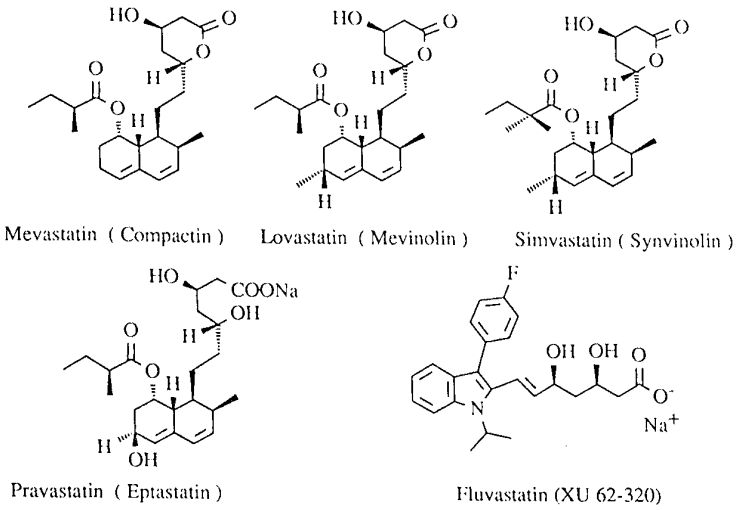
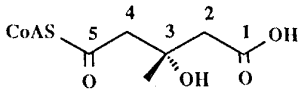


Figure 1

old. While all intensive studies hitherto conducted have been with closely related metabolites, such as compactin, mevinolin, and CS-514 (pravastatin), derived from fungal broths, efforts at the Sandoz Research Institute towards the development of new HMG-CoA reductase inhibitors have been based on synthesis, guided by the following assumptions:

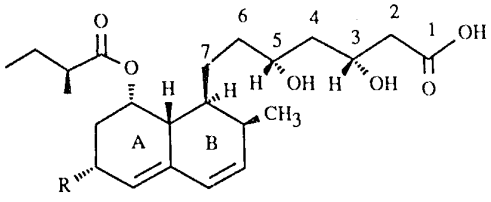
(a) There are two regions at the active site of the enzyme: one with high specific recognition of a 5-carbon unit (C-1 to C-5 as shown below) of the β-OH-β-Methyl-Glutaryl portion, and the other of CoA moiety present in HMG-CoA (Fig. 2).



HMG-CoA

Figure 2

(b) Compactin (R = H, Fig. 3), a known inhibitor of the enzyme, may be regarded as a transition state analog, when in the open dihydroxy acid form.



Compactin (R= H)

Figure 3

The 5-carbon unit of the side chain present in compactin (Fig. 3) probably occupies the same region as the 5-carbon unit in HMG-CoA (Fig. 2); the bicyclic A-B-ring system, with its substituents in compactin (Fig. 3), possibly sits in the same region or very close to the same region the CoA portion of the substrate HMG-CoA occupies at the active site of the enzyme. However, it is difficult to see any similarity in structure between the bicyclic-ring system of compactin and CoA, when one examines the structure of CoA shown in Fig. 4.

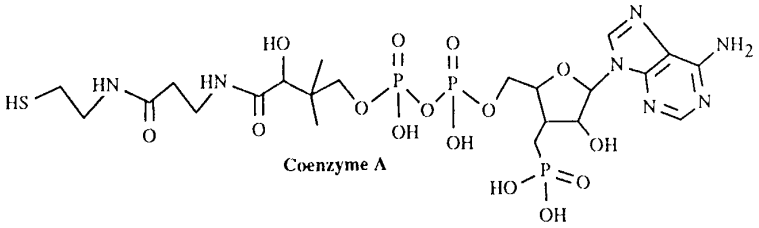
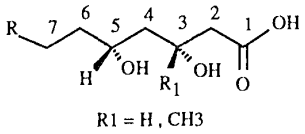


Figure 4

In light of (a) and (b) above, one hoped that it might possible to prepare interesting synthetic inhibitors of HMG-CoA reductase with a very general structure as shown in Fig. 5, with the 5-carbon unit (C-1 to C-5) preferably possessing the absolute configurations of C-3-OH and C-5-OH as present in compactin.

Choice of R and R_1 in Fig. 5 has depended on:



R1 = H , CH3

Figure 5

(a) Consideration of the elements of structure of CoA.

(b) Considerations of the overall shape and assumptions of the importance of substituents on Ring A-B of compactin (Fig. 3), first with molecular models and later with computer modelling.

(c) Exploiting the knowledge gained in structure activity relationships with our own Sandoz Research Institute compounds or being reported in literature by outside investigators.

Efforts with the above considerations in mind have led to the development of a variety of novel HMG-CoA reductase inhibitors. Synthesis and Structure Activity Relationships (SAR) of some of these novel inhibitors are discussed below with emphasis on the Phase III candidate, fluvastatin (XU 62-320): [R*,S*-(E)]-(±)-Sodium-3,5-dihydroxy-7-[3-(4-fluorophenyl)-1-(1-methyl-ethyl-1H-indol-2-yl]-hept-6-enoate (Fig. 1), a mevalonic acid analog more potent than compactin and lovastatin.

III. GENERAL CHEMISTRY APPROACH

Guided by the conviction that the C-3, C-5 dihydroxy acid fragment was the key pharmacophore necessary for the inhibition of HMG-CoA reductase,

our synthetic approach towards the synthesis of compounds of generic structure (Fig. 5) involved:

(a) A convergent synthesis coupling chiral Synthon 1 or racemic or chiral (3R, 5S) C-3, C-5-dihydroxy ester Synthon 2 with a variety of aryl or alkyl fragments 3 (Fig. 6), or

(b) A linear synthesis of the C-3, C-5 dihydroxy acid derivatives wherein the aldehyde 4 is reacted with acetoacetate 5 (Fig. 7) to provide a hydroxyketo ester intermediate, which, with subsequent steps, gives the desired final products of Fig. 5.

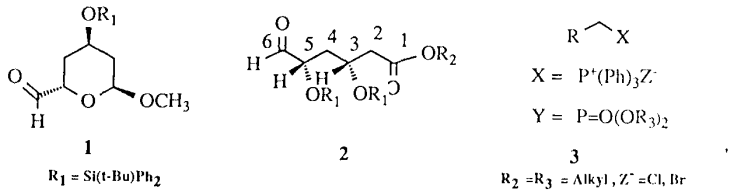


Figure 6

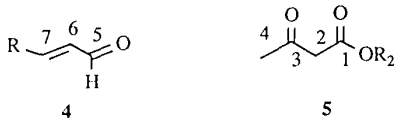
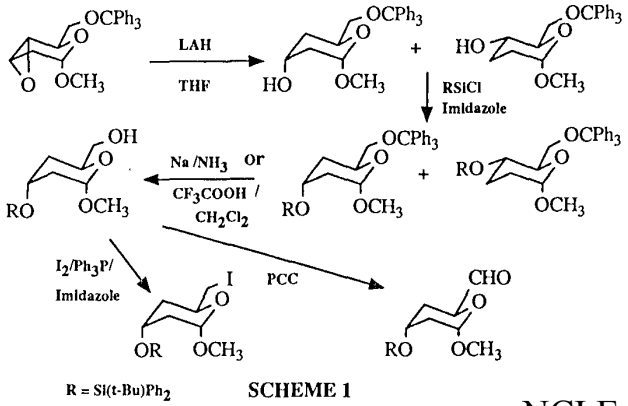


Figure 7

A. Synthesis of Synthon 1 and 2, Fig. 6 (Scheme 1 and Scheme 2)

Synthon 1 has been synthesized starting from D-glucose via the key lithium aluminum hydride reductive opening of the epoxide as depicted in Scheme 1.[5] The desired axial alcohol could be separated from the equatorial isomer by preparation of the silyl derivatives. The protected axial alcohol on PCC oxidation gave the desired lactol aldehyde.



SCHEME 1

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