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Volume 12

TRENDS IN MEDICINAL CHEMISTRY '88

Proceedings of the Xth International Symposium on Medicinal Chemistry, Budapest, 15–19 August 1988

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ELSEVIER — Amsterdam — Oxford — New York — Tokyo 1989

ELSEVIER SCIENCE PUBLISHERS B.V.
Sara Burgerhartstraat 25
P.O. Box 211, 1000 AE Amsterdam, The Netherlands

Distributors for the United States and Canada:

ELSEVIER SCIENCE PUBLISHING COMPANY INC.
655, Avenue of the Americas
New York, NY 10010, U.S.A.

ISBN 0-444-87380-5 (Vol. 12)
ISBN 0-444-41564-5 (Series)

Printed in The Netherlands

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Trends in Medicinal Chemistry '88

EXCITING DEVELOPMENTS IN THE AREA OF HMG-CoA REDUCTASE INHIBITORS

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SUMMARY

Investigations by Akira Endo with compactin, a potent inhibitor of HMG-CoA reductase, have to be largely credited for the resurgence of the research on cholesterol biosynthesis and the search for novel HMG-CoA reductase inhibitors. HMG-CoA reductase catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol. Considerations of the structural elements of the substrate (β-Hydroxy-β-Methyl-Glutaryl-CoA) and compactin involved in interactions at the active site of the enzyme, have guided the efforts at Sandoz Research Institute towards the development of a variety of novel HMG-CoA reductase inhibitors. Synthesis and Structure Activity Relationships (SAR) of these novel inhibitors are discussed with emphasis on the clinical candidate XU 62-320: [R*,S*-(E)]-(±)-Sodium-3,5-dihydroxy-7-[3-(4-fluorophenyl)-1-(1-methylethyl)-1 H-indol-2-yl]-hept-6-enoate, a mevalonic acid analogue more potent than compactin and Lovastatin.

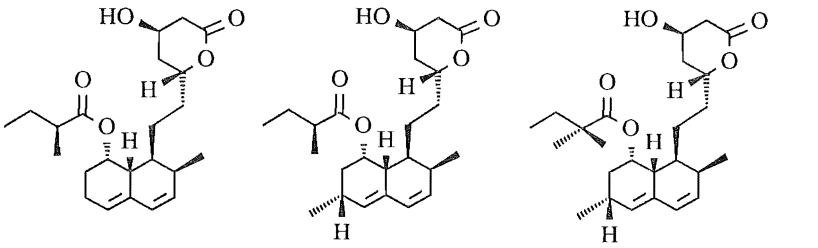
INTRODUCTION

Coronary heart disease is responsible for approximately 500,000 deaths each year in the United States and is associated with direct and indirect cost of more than $60 billion a year (Ref. 1). A large body of clinical and epidemiological data has linked elevation of blood cholesterol levels as a major cause of coronary heart disease. It has been established that lowering of low-density lipoprotein (LDL) cholesterol levels will reduce the risk of coronary heart disease in men with elevated blood cholesterol levels.

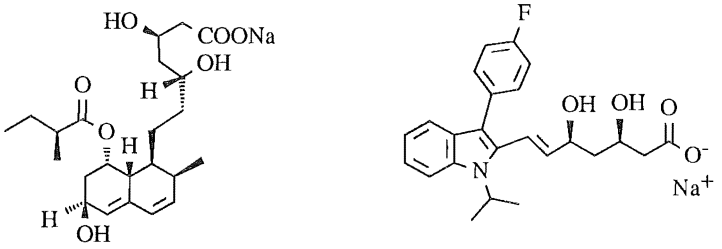
The need for the development of effective and safe therapeutic agents for the treatment of hyperlipoproteinemia has gained considerable support as a result of two important events: (1) the results of the Lipid Research Clinic's Coronary Primary Prevention Trial (LRC-CPPT), a multicenter, randomized, double-blind study involving 3,806 asymptomatic middle-aged men in the United States with type II hyperlipoproteinemia, which demonstrated that a statistically significant reduction of 19% in the rate of fatal plus non-fatal coronary heart disease was associated with a 9% decrease in blood cholesterol levels (Ref. 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 (Ref. 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), mevinolin (Lovastatin, Mevacor®) and Synvinolin (Simvastatin) (Ref. 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 forms the basis for initiating efforts at the Sandoz Research Institute for a variety of HMG-CoA reductase inhibitors with chemical structures different in several respects from compactin, Pravastatin (a hydroxy analogue of compactin), Lovastatin (a methyl analogue of compactin) and Simvastatin (a dimethyl analogue of compactin) and has led to XU 62-320, the first totally synthetic HMG-CoA reductase inhibitor for studies in human clinical trials (Fig. 1).



Mevastatin (Compactin) Lovastatin (Mevinolin) Simvastatin (Synvinolin)



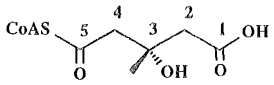
Pravastatin (Eptastatin) **Fig . 1** XU 62-320

DESIGN ASPECT

Investigations by Akira Endo with compactin (Ref. 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 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

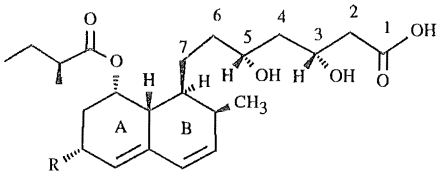
portion and the other of CoA moiety present in HMG-CoA.



HMG-CoA

Fig. 2

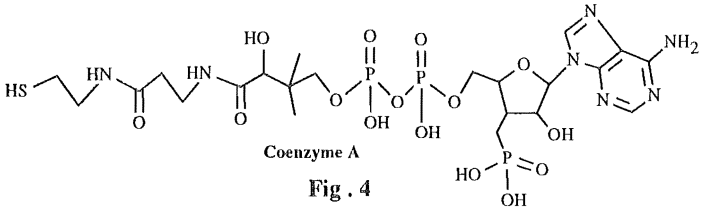
b) Compactin (R = H, Fig. 3), a known inhibitor of the enzyme, may be regarded as a transition state analogue, when in the open dihydroxy acid form.



Compactin (R= H)

Fig . 3

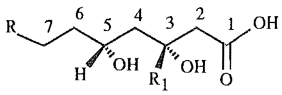
The 5-carbon unit of the side chain present in compactin (Fig. 3) probably occupies the same region as the 5-carbon unit in HMG-CoA (Fig. 2); the bicyclic A-B-ring system with its substituents in compactin (Fig. 3) possibly sits in the same region or very close to the same region the CoA portion of the 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 below (Fig. 4).



Coenzyme A

Fig . 4

In light of the above a) and b), one hoped that it might possible to prepare interesting synthetic inhibitors of HMG-CoA reductase with a very general structure as shown below 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.



R1 = H , CH3

Fig . 5

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