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1 The Discovery and Development of Atorvastatin, a Potent Novel Hypolipidemic Agent

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ABSTRACT

The search for potent and efficacious inhibitors of the enzyme HMG-CoA reductase (HMGRI) was the focus of considerable research in the 1980s. Building on the discovery of the fungal metabolite-derived inhibitors, mevastatin, lovastatin, pravastatin and simvastatin, a number of totally synthetic inhibitors were discovered and developed. This manuscript describes the discovery and development of one of those synthetic inhibitors, atovastatin calcium, currently marketed in the United States as LIPITOR®. This inhibitor was designed based in part on molecular modeling comparisons of the structures of the fungal metabolites and other synthetically derived inhibitors. In addition to development of the structure-activity relationships which led to atorvastatin calcium, another critical aspect of the development of this area was the parallel improvement in the chemistry required to prepare compounds of the increased synthetic complexity needed to potently inhibit this enzyme. Ultimately, the development of several chiral syntheses of enantiomerically pure atorvastatin calcium was accomplished through a collaborative effort between discovery and development. The impact of the progress of the required chemistry as well as external factors on internal decision-making with regards to the development of atorvastatin calcium will be discussed.

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The biosynthesis of cholesterol from acetyl-CoA involves a process of more than 20 biosynthetic steps *(Figure 1.1)* [1]. This tightly controlled pathway is regulated by the levels of low-density lipoprotein (LDL)-receptors on liver cells as the means of ensuring whole-body cholesterol homeostasis [2]. It has been known since the late 1950's and early 1960's that inhibition of cholesterol biosynthesis was an effective means of lowering plasma cholesterol in both animals [3] and man [4]. What was unclear was whether it could be done safely. In fact there were many doubts based on the experience with the triparanol (MER-23, **1**, *Figure 1.2*) which caused cataracts in humans [5]. Despite this setback, the criteria for a safe and effective inhibitor of cholesterol bio-

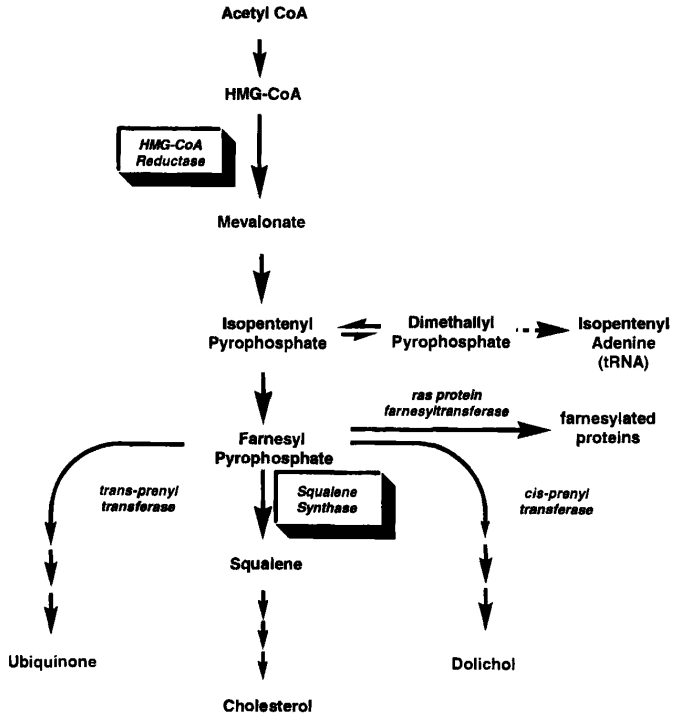

Figure 1.1. The Cholesterol biosynthetic pathway.

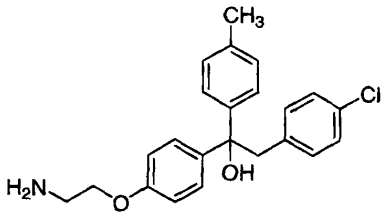

Figure 1.2. Triparanol (MER-29).

synthesis were clearly articulated by Curran and Azarnoff in 1957 [6]. Their postulate was that safe inhibition could be achieved by blocking the pathway after the formation of acetoacetate, but prior to the formation of squalene. When in-depth mechanistic studies were performed with triparanol, not surprisingly, it was discovered that it broke this rule by inhibiting the pathway at the pentultimate step in the biosynthetic pathway, as evidenced by the accumulation of desmosterol in the plasma and tissues of patients treated with this drug [7]. Further studies demonstrated that it was also desmosterol which accumulated in the lens of patients [8], emphasizing the potential dangers of inhibiting steps late in the biosynthetic pathway and causing medical concerns that would follow this area of research for decades. In fact, as recently as 1992, there were calls for a moratorium on the use of cholesterol-lowering drugs in primary prevention of myocardial infarction (MI) due to the lack of data from long-term clinical trials demonstrating a reduction not just in cardiovascular mortality, but in total mortality as well [9]. This concern was not completely alleviated until the results of the Scandinavian Simvastatin Survival Study were published in 1994 demonstrating reductions in total mortality with long-term statin treatment [10].

Despite the findings with triparanol, the search for cholesterol biosynthesis inhibitors continued unabated fueled by the hope that inhibition pre-squalene would avoid the formation of non-metabolizable sterol intermediates, such as desmosterol, and result in a safe and effect treatment for hypercholesterolemia [11].

The enzyme which became the focus of attention in the search for cholesterol biosynthesis inhibitors was 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGR, EC 1.1.1.34), the rate-limiting and first committed step in the biosynthetic pathway. This membrane-bound, endoplasmic reticulum localized enzyme catalyzes the two-step conversion of (*S*)-3-hydroxy-3-methylglutaryl-coenzyme A to 3-(*R*)-mevalonic acid through a putative hemi-thioacetal (*Figure 1.3*) [12]. Given that this hemi-thioacetal most likely represents a

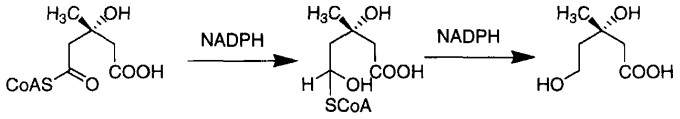

Figure 1.3. Reduction of HMG-CoA catalyzed by HMGR.

transition-state intermediate, it should not have been surprising when screening of fermentation beers resulted in the isolation of compounds that closely mimicked this structure.

The first fermentation product identified was isolated almost simultaneously by two separate laboratories and given the name compactin (later changed to mevastatin) by the Beecham group, who isolated it as an antifungal from strains of the microorganism *Penicillium brevicompactum* and determined its molecular structure by x-ray crystallography (**2**, *Figure 1.4*) [13]. The second group, from the Fermentation Research Laboratories at Sankyo, isolated the identical compound from cultures of *Penicillium citrinum*, but discovered it was a potent and competitive inhibitor of rat liver HMGR in vitro and sterol synthesis in vivo and gave it the code number ML-236B [14]. Further studies with ML-236B demonstrated that it decreased serum total and LDL-cholesterol in dogs [15], monkeys [16], and human patients with heterozygous familial hypercholesterolemia [17]. Shortly after the discovery of compactin, a second fungal metabolite (**3**), differing from compactin by a single methyl group was isolated from cultures of *Aspergillus terreus* by workers at Merck [18] (and named mevinolin) and from *Monascus ruber* by the Sankyo group (and named Monacolin K) [19]. This compound was found to inhibit rat liver HMGR twice as potently as compactin (Ki of 0.6 nM vs 1.4 nM) [18] and was later renamed lovastatin. Ultimately, **3** would be the first HMGR inhibitor (HMGRI) approved by the U.S. Food and Drug Administration for the treatment of hypercholesterolemia and would be marketed by Merck Sharpe and Dohme under the trade name Mevacor®. Two other potent fungal metabolite HMGRIs would ultimately become marketed drugs, pravastatin (**4**), produced by microbial hydroxylation of compactin [20] and simvastatin (**5**) produced by synthetic modification of lovastatin [21]. Although all of these compounds were potent HMGR inhibitors and effective cholesterol-lowering agents, in the early 1980's concern over the viability of these compounds was created by the termination of the development of compactin in 1980 due to safety concerns created by results from preclinical toxicology experiments [22]. This apparently also led to a temporary suspension of the development of lovastatin. Thus, even though the fungal metabolites as a class would ultimately prove extremely safe and effective in clinical trials, in the early 1980's there was at least a perceived need

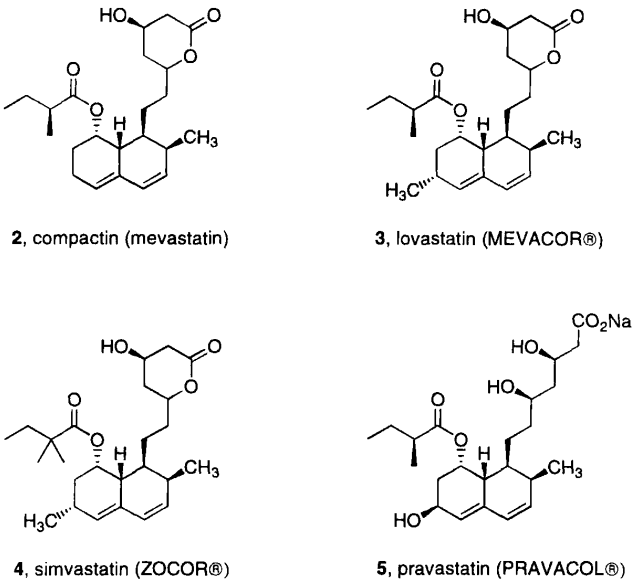

Figure 1.4. Fungal metabolite inhibitors of HMGR.

for structurally novel HMGR inhibitors such that any non-mechanism related toxicity would be avoided.

The first indication that the complex hexahydronaphthalene portion of the fungal metabolites could be replaced with a simpler ring system without loss of biological activity appeared in a patent application [23], then in publication form, from the Merck, Sharpe and Dohme Research Labs [24]. In this disclosure, it was revealed that ortho-biphenyl containing 3,5-dihydroxy-6-heptenoic acids and their lactones, such as **6** (*Figure 1.5*), were equipotent to the fungal metabolites at inhibiting HMGR in vitro. This disclosure led us to develop the hypothesis that the key requirements for potent inhibition of HMGR were a mevalonolactone/3,5-dihydroxy-heptanoic or -6-heptenoic acid moiety and a large lipophilic group held in the correct spatial relationship by a spacer or template group [25]. If this were true, then virtually any ring system which fulfilled this requirement would lead to a series of potent inhibitors. This hypothesis was apparently shared by other laboratories and a large number of

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