Recent Trends in the Design and Synthesis of New Antihypercholesterolemic Agents

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1. Introduction

Atherosclerosis and coronary heart disease(CHD), the leading cause of disability and death in the western world, are originated from the elevated level of plasma cholesterol, especially low-density lipoprotein(LDL).[1] Therapeutic reduction of serum cholesterol levels has been proven to be an effective treatment of atherosclerotic disease and agents to control plasma lipid levels have been sought as a potential therapy. So far, the major class of cholesterol lowering agents involves bile salt sequestrants, cholesterol absorption inhibitors, phenoxyacetic acid derivatives(fibric acid analogs), 3-hydroxy-3-methylglutaryl coenzyme A(HMG-CoA) reductase inhibitors, acyl-CoA: cholesterol *O*-acyltransferase (ACAT) inhibitors, and other HDL-elevating agents(nicotinic acid analogs, cholesteryl ester transfer protein(CETP) inhibitors, and lecithyl cholesterol *O*-acyltransferase(LCAT) inhibitors], *etc.*[2]

The evolution of cholesterol lowering agents based on design and synthesis as well as the researches on the structure-activity relationships(SAR) focussed on isosteric substitution of the lead compound will be discussed.

2. HMG-CoA Reductase Inhibitors[3]

A major new class of lipid-lowering drugs inhibits HMG-CoA reductase, the rate-limiting enzyme in the conversion of HMG-CoA to mevalonic acid. Over 70% of total body cholesterol in individuals is of endogenous origin, an attractive way to lower plasma cholesterol levels is, thus, to control *de novo* synthesis of cholesterol by selective

inhibition of biosynthetic step. The inhibition of HMG-CoA reductase, therefore, is the choice to control *de novo* synthesis of cholesterol. The discoveries of fungal metabolites mevastatin and lovastatin(Mevacor^{R}, Merck & Co, 1987) opened new era for the treatment of hypercholesterolemia by inhibiting cholesterol biosynthesis at the level of HMG-CoA reductase. The following development of pravastatin(Pravachol^{R}, Sankyo, 1989) and simvastatin(Zocor^{R}, Merck & Co, 1988), potent inhibitors of HMG-CoA reductase and currently in clinical use for the treatment of hypercholesterolemia, brought out focused efforts to develop novel HMG-CoA reductase inhibitors with improved properties by structural modification. Such an effort leads additional five additional statins such as fluvastatin (Locol^{R}, Norvatis, 1994), cerivastatin(Baycol^{R}, Bayer & Takeda, 1997), atrovastatin(Lipitor^{R}, Parke-Davis, 1997), and itavastatin(2000, approved in Europe by Sankyo, approval submitted in Japan by Kowa & Nissan) to the market. At this moment, two HMG-CoA reductase inhibitors, berivastatin(Lipha) and S-4522(Shionogi) are under clinical trials.

Inhibition of this key enzyme of cholesterol biosynthesis not only decreases the production of sterols but also enhances the expression of LDL receptors in the liver, thus, increasing the clearance of LDL from the body. Studies in mononuclear cells of normal subjects treated with the HMG-CoA reductase inhibitor also show a 4- to 5-fold increase in the amount of reductase activity. Such inhibitors increase HIM-CoA reductase mRNA levels and decreases enzyme degradation. Additionally, accelerated degradation of the reductase requires non-steroidal isoprenoids and sterols derived from mevalonic acid. Presumably, cells are finely tuned to maintain their cellular cholesterol levels within specific limits. As a result of inhibiting reductase activity with a competitive inhibitor of cholesterol biosynthesis, cells overcompensate and produce even more enzyme. An attractive area for future research is to design specific inhibitors of HMG-CoA reductase transcription. In this regard, oxysterols such as 25-hydroxycholesterol and 7-keto-cholesterol are potent inhibitors of reductase expression, and oxylanosterol intermediates may be useful for the inhibition of cholesterol biosynthesis.

3. ACAT Inhibitors[4]

Second class of cholesterol lowering agents is the inhibitors of ACAT. ACAT catalyzes the esterification of free cholesterol with fatty acyl-CoA to produce cholesteryl esters in the endoplasmic reticulum(ER), thus plays an important role in lipoprotein synthesis in intestine and liver and the cholesteryl esters formed from this reaction are used as a source of cholesterol for steroid synthesis in steroidogenic tissues. The major mechanism by which this class of compounds lowers plasma cholesterol levels is by blocking esterification of cholesterol in the intestinal mucosa thereby reducing chylomicron production. In the liver, delivery of cholesterol by the LDL receptor-mediated process upregulates the expression of ACAT. Presumably an ACAT inhibitor reduces the synthesis of VLDL in hepatic cells, thus, decreasing the production of LDL.

ACAT inhibitors are categorized into four major groups: i) fatty acyl amides, ii) disubstituted ureas, iii) cetaben sodium, and octmibates. Although a number of pharmaceutical companies have under development inhibitors of ACAT, most of the clinical trials are not as yet successful except melinamide(Artes oil^{R}, Sumimoto) due to poor efficacy and toxicity in adrenal glands of certain species. ACAT inhibitor F-1394 is in phase II clinical trials by Fusisawa, and Sankyo, recently, announced that their CS-505 is ready for phase II clinical trials. Several candidates are waiting for the clinical trials.

4. Fibric Acid Derivatives[5]

Another important class of hypolipidemic agents that affect VLDL metabolism are the fibric acid derivatives of which clofibrate(Atromid-S^{R}) and gemfibrozil(Lopid^{R}) are once the most widely used in the United States since 1960s. This class of compounds seems to have multiple mechanism of action. Clofibrate and gemfibrozil increase the amount of cholesterol secreted in the bile and appear to inhibit VLDL synthesis possibility by altering the synthesis of apoproteins. The major hypolipidemic effect of these fibric acid derivatives is their plasma triglyceride lowering activity by increasing lipoprotein lipase(LpL) activity. Although the sales of fibrates was decreased in 1980s, the development of second generation fibrates such as bezafibrate(Bezarip^{R}, Kisei, 1991), genofibrate(approval submitted in Japan by Sankyo, 1997), and fenofibrate(Lipindel^{R},

Grenan, 1999) opened new vista to the choletserol lowering agent.

5. Cholesterol Absorption Inhibitors[6]

The treatment of hypercholesterolemia through the inhibition of dietary and biliary cholesterol absorption is the more efficacious, well-tolerated method which regulates cholesterol homeostasis by complementary mechanisms of action, when combinated with other agents, such as statins. Corestatyl(approval submitted in USA by Jerutex), SCH-58235(Ezetimbe, Schering-Plough, phase III), GT-102-279(Jerutex, phase II), CP-88818(Pfizer, phase II), TA-7552(Tanabe, phase I), and MKC-121(Mitzubishi Tokyo, phase I) are under clinical trials.

6. HDL-Elevating Agents

Even though HMG-CoA reductase inhibitors, or stains, have become first line therapy for lowering plasma cholesterol levels, 58% to 76% of the statin-treated coronary heart disease(CHD) patients still did not experience therapeutic benefit, suggesting that a significant unmet medical need continues to exist for treating CHD. Studies on the treatment of CHD have shown that HDL-cholesterol is one of the best predictors of CHD risk, thus a safe and effective drug that raises HDL-cholesterol is needed. Many targets might raise HDL-cholesterol including enzymes associated with lipoprotein acyl transferase [e.g. hepatic triglyceride lipase, lipoprotein lipase, lecithyl cholesterol acyl transferase, or phospholipid transfer protein], modulating SR-B1(the hepatic HDL scavenger receptor), increasing apoAI or HDL apolipoproteins like apoAI Milano, or inhibiting cholesteryl ester transfer protein(CETP).[7]

Nicotinic acid, introduced to lower serum cholesterol level in 1955, is also a HDL elevating agent. Nicotinic acid additionally lowers serum triglycerides levels and is effective against hyperlipidemias Types II, III, IV, and V.

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